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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a **PROVISIONAL APPLICATION FOR PATENT** under 37 C.F.R. § 1.53(c).

	Docket Number	21108.0042U1	Type a Plus Sign (+) inside this box	+

INVENTOR(s)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (City and Either State or Foreign Country)
Yule	David	I.	33 Corral Drive, Penfield, New York 14526 (Citizenship: British)
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TITLE OF INVENTION (500 characters max)

INOSITOL 1,4,5-TRISPHOSPHATE RECEPTOR MUTANTS AND USES THEREOF

CORRESPONDENCE ADDRESS

Customer Number 23859

ENCLOSED APPLICATION PARTS (*Check All That Apply*)

- ☒ Provisional Application Title Page — *Number of Pages* [1]
- ☒ Specification (includes Description, Claims, & Abstract) — *Number of Pages* [54]
- ☒ Drawing(s) — *Number of Sheets* [16]
- ☒ Authorization to Treat Reply Requesting Extension of Time as Incorporating Petition for Extension of Time
- ☒ Other (specify): Sequence Listing (Paper Copy) [122 Pages] and Diskette

METHOD PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (*Check One*)	
☒ Applicant claims small entity status. See 37 CFR § 1.27. ☒ A Credit Card Payment Form PTO-2038 is enclosed to cover the filing fees. ☐ A check or money order is enclosed to cover the filing fees. ☐ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number _____. ☐ The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. _____.	**FILING FEE AMOUNT** $ 80.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☐ No.

☒ Yes. The name of the U.S. Government agency and the Government contract number are: National Institutes of Health, RO1-DK54568; RO1-DE14756 and PO1-DE13539

Respectfully submitted,

Signature Gwendolyn D. Spratt **Date** January 26, 2004

Typed or Printed Name: Gwendolyn D. Spratt

Registration No. 36,016

CERTIFICATE OF EXPRESS MAILING UNDER 37 C.F.R. § 1.10

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Michael Laird 1/26/04

Michael Laird Date

ATTORNEY DOCKET NO. 21108.0042U1
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
	)	
YULE et al.	)	Art Unit: Unassigned
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Application No. Unassigned	)	Examiner: Unassigned
	)	
Filing Date: Concurrently	)	Confirmation No. Unassigned
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For: INOSITOL 1,4,5-TRISPHOSPHATE RECEPTOR MUTANTS AND USES THEREOF	)	

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Sir:

Pursuant to 37 C.F.R. § 1.136(a)(3), the Commissioner is hereby requested and authorized to treat any concurrent or future reply in the above-identified application, requiring a petition for an extension of time for its timely submission, as incorporating a petition for extension of time for the appropriate length of time.

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PATENT

The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

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Michael Laird — Date: 1/26/04

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Attorney Docket No. 21108.0042U1

UTILITY PATENT - PROVISIONAL FILING

PROVISIONAL APPLICATION FOR LETTERS PATENT

TO ALL WHOM IT MAY CONCERN:

Be it known that we, David I. Yule and Larry Wagner, II, residing respectively at 33 Corral Drive, Penfield, New York 14526 and 276 Glen Ellyn Way, Rochester, New York 14618 have invented new and useful improvements in

INOSITOL 1,4,5-TRISPHOSPHATE RECEPTOR MUTANTS AND USES THEREOF

for which the following is a specification.

INOSITOL 1,4,5-TRISPHOSPHATE RECEPTOR MUTANTS AND USES THEREOF

This invention was made with government support under Grants RO1-DK54568; RO1-DE14756 and PO1-DE13539 awarded by the National Institutes of Health. The government has certain rights in the invention.

I. BACKGROUND OF THE INVENTION

1. Inositol 1,4,5-trisphosphate receptors are ubiquitous ligand-gated ion channels localized to the endoplasmic reticulum which function to couple activation of cell surface receptors to intracellular Ca^{2+} release [1]. Genes have been identified which encode three distinct proteins of molecular weight ~ 300 kDa and have been named the type 1,2 and 3 $InsP_3R$ [2-5] . Notably, the type-1 receptor gene is alternatively spliced to yield additional variants of the receptor, which have specific tissue distribution [6, 7]. The functional channel is a tetramer, consisting of a binding site for $InsP_3$ in the N-terminus of each subunit [8, 9], and a single calcium permeable pore, formed from six transmembrane spanning helices located towards the C-terminus of each subunit [10, 11]. Between these regions is a ~1600 amino acid cytoplasmic loop which is termed the regulatory and coupling domain.

2. This regulation of $InsP_3R$, together with the complement of $InsP_3R$ types and the sub-cellular localization of the channel, are thought to be the major determinants of the spatio-temporal characteristics of agonist-evoked Ca^{2+} signals [13, 14]. These particular characteristics likely contribute to the fidelity and specificity associated with activation of Ca^{2+}-dependent effectors. The most important regulator of $InsP_3$-induced Ca^{2+} release is Ca^{2+} itself [12, 15-17], however, numerous factors including adenine nucleotides [18, 19], protein interactions [12, 20] and phosphorylation by various kinases can significantly influence $InsP_3R$ function [7, 21-31]. In particular, since all $InsP_3R$ subtypes are phosphorylated by cAMP and cGMP-dependent protein kinases (PKA and PKG) [7, 21-23, 25, 26, 28, 29, 32-41], the $InsP_3R$ may represent an important nexus for cross-talk between these distinct signaling pathways. Indeed, cyclic nucleotide-dependent kinase-induced phosphorylation of $InsP_3R$ is proposed to be important in such diverse physiological and pathophysiological processes as synaptic plasticity [23], remodeling following neurotoxic insult [39], smooth muscle contractility [36, 37] and fluid secretion [29].

II. BRIEF DESCRIPTION OF THE DRAWINGS

3. The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description, serve to explain the principles of the invention.

4. Figure 1 shows the phosphorylation of S1755 results in enhanced Ca^{2+} release by $S2^+$ $InsP_3R$-1. In Figure 1A, DT40 3ko cells shown in the inset were transfected with M3 receptor, HcRed and $S2^+$ $InsP_3R$-1 as described below. Fura-2 loaded cells were stimulated with 50 nM Carbadol (CCh) to increase $[Ca^{2+}]_i$. A $[Ca^{2+}]_i$ increase was only evoked in cells expressing HcRed, and thus presumably M3 receptor and $S2^+$ $InsP_3R$-1 (compare black trace vs. gray trace from cells indicated in the inset). Treatment with 20 μM forskolin, to raise cAMP levels and activate PKA, resulted in a markedly enhanced CCh-induced $[Ca^{2+}]_i$ signal. After removal of forskolin a subsequent exposure to CCh resulted in a $[Ca^{2+}]_i$ increase similar to control. In Figure 1B, a similar experimental paradigm was utilized in DT-40 3ko cells expressing S1589A $S2^+$ $InsP_3R$-1. Stimulation with CCh following 20 μM forskolin also resulted in a markedly enhanced $[Ca^{2+}]_i$ increase relative to a control stimulation. Figure 1C shows that in cells expressing S1755A $S2^+$ $InsP_3R$-1, forskolin treatment did not result in an enhanced signal. Figure 1D shows pooled data from the number of cells indicated for each construct, showing the normalized fold increase in initial $[Ca^{2+}]_i$ peak over control resulting from forskolin treatment of cells expressing $S2^+$ $InsP_3R$-1 and serine to alanine mutants. Forskolin treatment resulted in CCh responses in Wild type and S1589A $S2^+$ $InsP_3R$-1 cells being significantly different from S1755A $S2^+$ $InsP_3R$-1 expressing cells. Cartoon inset depicts the $S2^+$ $InsP_3R$-1 regulatory and coupling domain. The black shaded region represents the S2 splice region. The functionally important phosphorylation of S1755 is indicated by a gray circle.

5. Figure 2 shows the potentiation of Ca^{2+} release by forskolin after flash photolysis of ci$InsP_3$-PM. DT-40 3ko cells expressing $S2^+$ $InsP_3R$-1 were loaded with the visible wavelength Ca^{2+} indicator Fluo-4 and the cell permeable caged $InsP_3$ analog ci$InsP_3$-PM as described below. Figure 2A shows minimal photolysis of $InsP_3$ was evoked by a brief UV flash, (~0.5 msec indicated by the arrows) resulting in a small increase in $[Ca^{2+}]_i$. A subsequent, identical flash of UV light 5 min. later fails to evoke a larger increase in $[Ca^{2+}]_i$, although increasing the duration of the flash to 5 ms evokes a significantly larger increase in $[Ca^{2+}]_i$ (arrow, "max uncage"). In Figure 2B, an identical protocol was followed except the second minimal uncaging was performed following 5 min. treatment with 10 μM forskolin.

This treatment resulted in a significantly larger increase in $[Ca^{2+}]_i$ when compared to the initial uncaging. Figure 2C shows pooled data comparing normalized fold increase for the first and second uncaging in the presence or absence of forskolin. Treatment with forskolin results in a statistically significant increase in the second response.

6. Figure 3 shows both S1589 and S1755 are functionally important PKA phosphorylation sites in S2$^-$ $InsP_3R$-1. A similar experimental paradigm as described in fig. 1 was utilized to assess the consequences and functionally important phosphorylation sites in S2$^-$ $InsP_3R$-1. Figure 3A shows treatment of wild type S2$^-$ $InsP_3R$-1 with forskolin resulted in enhanced CCh stimulated Ca^{2+} release with respect to a control CCh stimulation. Figure 3B shows a similar potentiation was observed with S1589A S2$^-$ $InsP_3R$-1 expressing cells. Figure 3C shows a similar enhanced $[Ca^{2+}]_i$ signal was observed following forskolin treatment in S1755A S2$^-$ $InsP_3R$-1 expressing cells. Figure 3D shows that no effect of forskolin treatment was observed in double mutant S1589A/S1755A S2$^-$ $InsP_3R$-1 expressing cells. Figure 3E shows pooled data for the number of cells indicated for each construct. The filled bars indicate data for the particular construct obtained using the low affinity Ca^{2+} indicator Fura-2FF. Normalized fold increase is only significantly altered in the double mutant. Cartoon inset depicts the functionally important phosphorylation of S1589 and S1755, indicated by gray circles.

7. Figure 4 shows the phosphorylation of S1755 by PKG results in enhanced Ca^{2+} release by S2$^+$ $InsP_3R$-1. A similar experimental paradigm utilized for experiments presented in fig. 1 was performed to assess the effects and site(s) of phosphorylation by PKG on S2$^+$ $InsP_3R$-1. Figure 4A shows treatment with 10 μM 8-Br cGMP to specifically activate PKG results in a marked potentiation of CCh-evoked Ca^{2+} release when compared to control CCh stimulation in the absence of PKG activation. Figure 4B shows a similar potentiation of Ca^{2+} release following PKG activation was observed in cells expressing S1589A S2$^+$ $InsP_3R$-1. Figure 4C shows that PKG activation does not enhance Ca^{2+} release by S1755A S2$^+$ $InsP_3R$-1. Figure 4D shows that PKG does not inhibit CCh-induced Ca^{2+} release by S1755A S2$^+$ $InsP_3R$-1. Figure 4E shows pooled data for the number of cells indicated for each construct. Normalized fold increase by S1755A S2$^+$ $InsP_3R$-1 was significantly different from both wild-type and S1589A S2$^+$ $InsP_3R$-1. Cartoon inset depicts the functionally important phosphorylation of S1755, indicated by a gray circle.

8. Figure 5 shows that treatment with PKI inhibits forskolin but not 8-Br cGMP-induced potentiation. Cells expressing S2$^+$ $InsP_3R$-1 were treated for 30 mins with myr-PKI(14-22) prior to assessing the effects of activating PKA or PKG. Figure 5A shows that

PKI treatment completely abolishes the forskolin-induced enhancement of Ca^{2+} release. Figure 5B shows that PKI does not affect the 8-Br cGMP-induced enhancement of Ca^{2+} release. Figure 5C shows the results of pooled data.

9. Figure 6 shows PKG activation is without effect on Ca^{2+} release by S2$^-$ $InsP_3R$-1. A similar experimental paradigm used in experiments depicted in fig. 1 was utilized to assess the effects of PKG phosphorylation of S2$^-$ $InsP_3R$-1. Figure 6A shows that PKG activation has no effect on CCh-evoked Ca^{2+} release by wild-type S2$^-$ $InsP_3R$-1. Figure 6B shows that similarly no effect was observed in S1589A S2$^-$ $InsP_3R$-1 expressing cells. Figure 6C shows that no effect was observed in S1755A S2$^-$ $InsP_3R$-1 expressing cells. Figure 6D shows pooled data for the number of cells indicated for each construct. Cartoon depicts absence of phosphorylation by PKG.

10. Figure 7 shows in Figure 7A that ATP treatment of fura-2 loaded mouse parotid acinar cells, in the presence of la^{3+} to block Ca^{2+} entry (isolating P2Y receptors) results in an increase in $[Ca^{2+}]_i$. The $[Ca^{2+}]_i$ is markedly enhanced by incubation with forskolin. Figure 7B shows that CCh treatment of human parotid acinar cells results in an increase in $[Ca^{2+}]_i$ which is potentiated by forskolin treatment. Representative traces from >4 experiments and >3 preparations of tissue.

11. Figure 8A depicts representative traces showing that mutation of both functional phosphorylation sites in the short form of $InsP_3R$-1 to glutamate residues results in a receptor which is apparently more sensitive to $InsP_3$ as revealed by increased sensitivity to CCh. Figure 8B shows the pooled data illustrating that the S1589E/S1755E mutant $InsP_3R$-1is approximately 7.5 fold more sensitive than the wild type S2- $InsP_3R$-1 and approximately 35 fold more sensitive than the S1589A/S1755A nonphosphorylatable S2- $InsP_3R$-1

12. Figure 9 shows single channel records from an isolated Cos-7 cell nucleus patched on several occasions. K^+ is the charge carrier, holding potential was +20 mV. Channel activity is observed only when $InsP_3$ is present in the pipette. Note in the final trace several channels appear to be present. Representative of 7 experiments.

13. Figure 10 shows a cartoon depicting the proposed structure of the $InsP_3R$.

14. Figure 11 depicts the regulatory and coupling domain of the $InsP_3R$-1; showing the phosphorylation sites at S1589 and S1755. In addition the location of the S2 splice site is shown.

15. Figure 12A shows that single mutation of S1589E in S2+ $InsP_3R$ has little effect on the potentiation of Ca^{2+} signaling seen upon phosphorylation of the receptor, confirming in

the S2+ variant of the receptor that this site is not functional. Figure 12B/C show that stimulation of cells expressing the S1755E phosphomimetic mutation are apparently more sensitive to stimulation, and in additon no further enhancement of Ca^{2+} signaling is observed following PKA activation, confirming S1755 as the functionally important site.

16. Figure 13A/B shows that if either S1589 or S1755 is mutated to glutamate individually that no further potentiation by PKA stimulation is observed. Indicating that phosphorylation of individual sites is not functionally additive.

17. Figure 14 shows that $InsP_3R$-III can be phosphorylated in a PKA dependent fashion.

18. Figure 15A shows stimulation of DT40 cells expressing chicken $InsP_3$ R-III results in Ca^{2+} oscillations. Figure 15B shows that activation of PKA during these oscillations results in an inhibition of the Ca^{2+} signal, consistent with an effect on the $InsP_3R$-III.

19. Figure 16 shows that stimulation of DT-40 3ko transfected with rat $InsP_3R$-III results in Ca^{2+} signals which are inhibted by stimulating PKA.

III. DETAILED DESCRIPTION

20. The present invention may be understood more readily by reference to the following detailed description of preferred embodiments of the invention and the Examples included therein and to the Figures and their previous and following description.

21. Before the present compounds, compositions, articles, devices, and/or methods are disclosed and described, it is to be understood that this invention is not limited to specific synthetic methods, specific recombinant biotechnology methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

Definitions

22. In this specification and in the claims which follow, reference will be made to a number of terms which shall be defined to have the following meanings:

23. As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like.

24. Ranges may be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be

understood that the particular value forms another embodiment. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as "about" that particular value in addition to the value itself. For example, if the value "10" is disclosed, then "about 10" is also disclosed. It is also understood that when a value is disclosed that "less than or equal to" the value, "greater than or equal to the value" and possible ranges between values are also disclosed, as appropriately understood by the skilled artisan. For example, if the value "10" is disclosed the "less than or equal to 10"as well as "greater than or equal to 10" is also disclosed.

25. "Treatment" or "treating" means to administer a composition to a subject with an undesired condition or at risk for the condition. The condition can be any pathogenic disease, autoimmune disease, cancer or inflammatory condition. The effect of the administration of the composition to the subject can have the effect of but is not limited to reducing the symptoms of the condition, a reduction in the severity of the condition, or the complete ablation of the condition.

26. By "effective amount" is meant a therapeutic amount needed to achieve the desired result or results, e.g., increasing or decreasing Ca^{2+} release, enhancing or blunting physiological functions, altering the qualitative or quantitative nature of the proteins expressed by cell or tissues, and eliminating or reducing disease causing molecules and/or symptoms.

27. "Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

28. By "subject" is meant an individual. Preferably, the subject is a mammal such as a primate, and, more preferably, a human. The term "subject" can include domesticated animals, such as cats, dogs, etc., livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), and laboratory animals (e.g., mouse, rabbit, rat, guinea pig, etc.).

29. By "$InsP_3R$" is meant an inositol 1,4,5-triphosphate receptor. Such receptors are generally the major route of intracellular calcium release in eukaryotic cells and are pivotal for stimulation of calcium dependent effectors. Modulation of calcium release through these receptors has important consequences in a development and in a variety of normal and pathological cellular conditions. There are three major types of $InsP_3R$: $InsP_3R$-1, $InsP_3R$-2, and $InsP_3R$-3. $InsP_3R$-1 has two major splice variants: the $S2^-$ and the $S2^+$. The $S2^-$ splice

variant of $InsP_3R$-1 is the short splice variant in which 40 amino acids are excised. Specifically, residues 1693 to 1732 of the full length variant (ie. $S2^+$ or the long splice variant) are excised. The $S2^-$ variant is located predominantly in peripheral tissues whereas the $S2^+$ variant is present predominantly in the CNS.

30. By "homology" is meant the degree of relatedness shared between two or more nucleic acids, peptides, polypeptides or proteins as determined by their sequence structure or function.

31. It is understood that as discussed herein the use of the terms homology and identity mean the same thing as similarity. Thus, for example, if the use of the word homology is used between two non-natural sequences it is understood that this is not necessarily indicating an evolutionary relationship between these two sequences, but rather is looking at the similarity or relatedness between their nucleic acid sequences. Many of the methods for determining homology between two evolutionarily related molecules are routinely applied to any two or more nucleic acids or proteins for the purpose of measuring sequence similarity regardless of whether they are evolutionarily related or not.

32. In general, it is understood that one way to define any known variants and derivatives or those that might arise, of the disclosed genes and proteins herein, is through defining the variants and derivatives in terms of homology to specific known sequences. This identity of particular sequences disclosed herein is also discussed elsewhere herein. In general, variants of genes and proteins herein disclosed typically have at least, about 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 percent homology to the stated sequence or the native sequence. Those of skill in the art readily understand how to determine the homology of two proteins or nucleic acids, such as genes. For example, the homology can be calculated after aligning the two sequences so that the homology is at its highest level.

33. Another way of calculating homology can be performed by published algorithms. Optimal alignment of sequences for comparison may be conducted by the local homology algorithm of Smith and Waterman Adv. Appl. Math. 2: 482 (1981), by the homology alignment algorithm of Needleman and Wunsch, J. MoL Biol. 48: 443 (1970), by the search for similarity method of Pearson and Lipman, Proc. Natl. Acad. Sci. U.S.A. 85: 2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by inspection.

34. The same types of homology can be obtained for nucleic acids by for example the algorithms disclosed in Zuker, M. *Science* 244:48-52, 1989, Jaeger et al. *Proc. Natl. Acad. Sci. USA* 86:7706-7710, 1989, Jaeger et al. *Methods Enzymol.* 183:281-306, 1989 which are herein incorporated by reference for at least material related to nucleic acid alignment. It is understood that any of the methods typically can be used and that in certain instances the results of these various methods may differ, but the skilled artisan understands if identity is found with at least one of these methods, the sequences would be said to have the stated identity, and be disclosed herein.

35. For example, as used herein, a sequence recited as having a particular percent homology to another sequence refers to sequences that have the recited homology as calculated by any one or more of the calculation methods described above. For example, a first sequence has 80 percent homology, as defined herein, to a second sequence if the first sequence is calculated to have 80 percent homology to the second sequence using the Zuker calculation method even if the first sequence does not have 80 percent homology to the second sequence as calculated by any of the other calculation methods. As another example, a first sequence has 80 percent homology, as defined herein, to a second sequence if the first sequence is calculated to have 80 percent homology to the second sequence using both the Zuker calculation method and the Pearson and Lipman calculation method even if the first sequence does not have 80 percent homology to the second sequence as calculated by the Smith and Waterman calculation method, the Needleman and Wunsch calculation method, the Jaeger calculation methods, or any of the other calculation methods. As yet another example, a first sequence has 80 percent homology, as defined herein, to a second sequence if the first sequence is calculated to have 80 percent homology to the second sequence using each of calculation methods (although, in practice, the different calculation methods will often result in different calculated homology percentages).

Mutants

36. The present invention provides mutant receptor proteins of two general categories: phosphomimetic mutant $InsP_3$ receptors and nonphosphorylatable mutant $InsP_3$. By "phosphomimetic" is meant a receptor that has an increased Ca^{2+} release function as compared to the wild-type $InsP_3R$ as a result of amino substitution to mimic phosphorylation. Preferably, the phosphomimetic mutant has a Ca^{2+} release function that is 3, 4, 5, 6, 7, 8, 9, 10 (or any amount in between) times that of the corresponding wild-type receptor. Preferably, the phosphomimetic mutant has a Ca^{2+} release function that is 10, 20,

30, 40 (or any amount in between) times that of the corresponding nonphosphorylatable mutant. By "nonphosphorylatable" mutant is meant a "null" mutant that is not phosphorylated under conditions that cause phosphorylation in the wild-type. The mutants can be derived from $InsP_3R$-1, either the $S2^-$ or the $S2^+$ variant; $InsP_3R$-2; or $InsP_3R$-3.

37. By increased or enhanced Ca^{2+} release function is meant an increase release of calcium following a stimulus that activates the $InsP_3R$. Such stimuli include, for example, carbachol, an analog of acxetylcholine, acting at muscarinic M3 receptors or alternatively, any agonist acting at any one of over one hundered plasma membrane receptors for neurotransmitters, hormones and growth factors coupled to the formation of $InsP_3$. In addition ehanced Ca^{2+} release can occur following direct activation of $InsP_3R$ with $InsP_3$ or its analogs.

38. The phosphomimetic mutants are derived by substitution of a serine in a phosphorylation site with a negatively charged amino acid residue. "By substitution of a serine in a phosphorylation site with a different amino acid residue" is meant that serine is removed and the different amino acid residue replaces it. By "a negatively charged amino acid residue" is meant that when incorporated into the protein it provides a net negative charge at the phosphorylation site. Thus, the substitution with the negatively charged amino acid residue neutralizes the positive charge at the site (provided at least by the typical arginine residue at the phosphorylation site). The phosphorylation site can be the strong PKA recognition motif of RXXS (SEQ ID NO:21), in which X represents any amino acid.. The serine residue can be replaced with either aspartate or glutamate. Thus the invention provides a $InsP_3R$ mutant comprising at least one substitution of serine for a negatively charged amino acid residue at a phosphorylation site of a wild-type $InsP_3R$, wherein the mutant has an enhanced Ca^{2+} release function as compared to the wild-type $InsP_3R$. Preferably the mutant's Ca^{2+} release function is at least 5 times greater than the Ca2+ release function of the wild-type $InsP_3R$. Preferably the mutant's Ca^{2+} release function is at least 10 times greater than the Ca^{2+} release function of the wild-type $InsP_3R$.

39. The invention provides a phosphomimetic $InsP_3R$-1 mutant, which has enhanced Ca^{2+} release function as compared to the wild-type $InsP_3R$-1. More specifically, the mutant comprises at least one substitution of serine for a negatively charged amino acid residue at a phosphorylation site, wherein the phosphorylation site is selected from residue 1589 or 1755 of a wild–type $InsP_3R$ sequence. As used throughout, the amino acid residues are numbered according to the rat sequences for the full length $InsP_3R$. Thus, one of skill in the art, can readily align the sequence for human (ATCC Acc. No. NM_002222), mouse (ATCCAcc.

No. NM_010585), or any other species and replace the comparable serine residue with the desired amino acid.

40. Examples of $InsP_3R$-1 phosphomimetic mutants include those wherein the substitution of serine for the negatively charged amino acid (including either glutamate or aspartate) is at residue 1589. Thus the mutant can comprise the amino acid sequence of SEQ ID NO:1, which corresponds to the short splice variant S1589E; SEQ ID NO:2, which corresponds to the long splice variant for S1589E; SEQ ID NO:3, which corresponds to S1589D in the short splice variant; SEQ ID NO:4, which corresponds to the long splice variant of S1589D.

41. The invention also provides the amino acids of SEQ ID NO:1,2,3,or 4 having one or more conservative amino acid substitutions, wherein the Ca^{2+} release function is maintained. Also provided are mutants comprising amino acid sequences having at least 80, 85, 90, 95, 96, 97, 98, 99 % (or any amount in between these values) homology to the amino acid sequence of SEQ ID NO:1,2,3,or 4 wherein the Ca^{2+} release function is maintained. Also provided are the comparable S1589E and S1589D mutants for various species.

42. Examples of $InsP_3R$-1 phosphomimetic mutants include those wherein the substitution of serine for the negatively charged amino acid (including either glutamate or aspartate) is at residue 1755. Thus the mutant can comprise the amino acid sequence of SEQ ID NO:5; which corresponds to the short variant of S1755E; SEQ ID NO:6, which corresponds to the long splice variant of S1755E; SEQ ID NO:7, which corresponds to the short variant of S1755D; and SEQ ID NO:8, which corresponds to the long splice variant of S1755D.

43. The invention also provides the amino acids of SEQ ID NO: 5, 6, 7, and 8 having one or more conservative amino acid substitutions, wherein the Ca^{2+} release function is maintained. Also provided are mutants comprising amino acid sequences having at least 80, 85, 90, 95, 96, 97, 98, 99 % (or any amount in between these values) homology to the amino acid sequence of SEQ ID NO:5,6,7, or 8, wherein the Ca^{2+} release function is maintained. Also provided are the comparable S1755E and S1755D mutants for various species.

44. The invention also provides a $InsP_3R$-1 mutant, wherein the substitutions of serine for the negatively charged amino acid is at residues 1589 and 1755. Either glutamate or aspartate is substituted for the two serines, in any combination. Thus, the invention provides a mutant, wherein glutamate is substituted for serine at residues 1589 and 1755;

including for example a mutant comprising the amino acid sequence of SEQ ID NO:9, which corresponds to the S1589E/S1755E mutant of the short splice variant, or SEQ ID NO:10, which corresponds to the S1589E/S1755E mutant of the long splice variant. The invention also provides a mutant, wherein aspartate is substituted for serine at residues 1589 and 1755, including for example a mutant comprising SEQ ID NO:11, which corresponds to S1589D/S1755D of the short splice variant; SEQ ID NO:12, which corresponds to S1589D/S1755D of the long splice variant.

45. The invention also provides the amino acids of SEQ ID NO: 9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12 having one or more conservative amino acid substitutions, wherein the Ca^{2+} release function is maintained. Also provided are mutants comprising amino acid sequences having at least 80, 85, 90, 95, 96, 97, 98, 99 % (or any amount in between these values) homology to the amino acid sequence of SEQ ID NO:9, 10, 11, or 12, wherein the Ca^{2+} release function is maintained. Also provided are the comparable S1589E/S1755E and S1589D/S1755D mutants for various species.

46. The invention further provides double mutants, wherein aspartate is substituted for serine at residue 1589 and glutamate is substituted for serine at residue 1755. For example, the invention provides a mutant comprising the amino acid sequence of SEQ ID NO:13, which corresponds to S1589D/S1755E short splice variant; and SEQ ID NO:14, which corresponds to a S1589D/S1755E mutation in the long splice variant. The invention also provides a mutant, wherein glutamate is substituted for serine at residue 1589 and aspartate is substituted for serine at residue 1755; including, for example, a mutant comprising the amino acid of SEQ ID NO:15, which corresponds to a S1589E/S1755D mutant of the short splice variant; and a mutant comprising the amino acid of SEQ ID NO:16, which corresponds to a S1589E/S1755D mutation in the long splice variant.

47. The invention also provides the amino acids of SEQ ID NO: 13, 14, 15, 16, having one or more conservative amino acid substitutions, wherein the Ca^{2+} release function is maintained. Also provided are mutants comprising amino acid sequences having at least 80, 85, 90, 95, 96, 97, 98, 99 % (or any amount in between these values) homology to the amino acid sequence of SEQ ID NO:13, 14, 15, or 16, wherein the Ca^{2+} release function is maintained. Also provided are the comparable S1589D/S1755E and S1589E/S1755D mutants for various species.

48. Similar to those outlined above for the $InsP_3R$-1 mutant, the invention provides phosphomimetic $InsP_3R$-2 mutants. More specifically, the mutant comprises at least one substitution of serine for a negatively charged amino acid residue at a phosphorylation site,

wherein the phosphorylation site is selected from residues 766, 1772, 1856, 1772, 1856, 2058, or 2227. For example, the sequence of SEQ ID NO:19 can be modified to form S766E, S766D, S1772D, S1772E, S1856E, S1856D, S2058E, S2058D, S2227E, S2227D. Furthermore, any combination of these serine substations can be made to form mutants with two, three, four, or five different substitutions. As for the $InsP_3R$-1 mutants, the invention further provides substitution $InsP_3R$-1 mutants wherein the amino acid sequence modified from the wild type sequence, provided herein as SEQ ID NO:19, has one or more conservative amino acids, wherein the Ca^{2+} release function is maintained. Also provided are mutants comprising amino acid sequences having at least 80, 85, 90, 95, 96, 97, 98, 99 % (or any amount in between these values) homology to the amino acid sequence modified from the wild type sequence (provided herein as SEQ ID NO:19), wherein the Ca^{2+} release function is maintained. Also provided are the comparable $InsP_3R$-2 mutants for various species designed by aligning the $InsP_3R$-2 of the species with the rat species an substituting the corresponding amino acid sequence.

49. Similar to those outlined above for the $InsP_3R$-1 mutant, the invention provides phosphomimetic $InsP_3R$-3 mutants. More specifically, the mutant comprises at least one substitution of serine for a negatively charged amino acid residue at a phosphorylation site, wherein the phosphorylation site is selected from residues 934, 1640, 1834, 2009, 2041, or 2189. For example, the sequence of SEQ ID NO:20 can be modified to form S934E, S934D, S1640D, S1640E, S1834E, S1834D, S2009E, S2009D, S2041E, S2041D, S2189E, or S2189D. Furthermore, any combination of these serine substations can be made to form mutants with two, three, four, five, or six different substitutions. As for the $InsP_3R$-1 mutants, the invention further provides substitution $InsP_3R$-1 mutants wherein the amino acid sequence modified from the wild type sequence, provided herein as SEQ ID NO:20, has one or more conservative amino acids, wherein the Ca^{2+} release function is maintained. Also provided are mutants comprising amino acid sequences having at least 80, 85, 90, 95, 96, 97, 98, 99 % (or any amount in between these values) homology to the amino acid sequence modified from the wild type sequence (provided herein as SEQ ID NO:20), wherein the Ca^{2+} release function is maintained. Also provided are the comparable $InsP_3R$-2 mutants for various species designed by aligning the $InsP_3R$-2 of the species with the rat species and substituting the corresponding amino acid sequence.

50. The invention also provides mutants that are nonphosphorylatable. Specifically, the invention provides an $InsP_3R$ mutant comprising at least one substitution of serine for an amino acid with an aliphatic side chain at a phosphorylation site of a wild-type $InsP_3R$,

wherein the mutant is nonphosphorylatable. Preferably, the amino acid with the aliphatic side chain is alanine. The mutant can be a modified $InsP_3R$-1 (either the long or short splice variant), $InsP_3R$-2, or $InsP_3R$-3. Thus, the sequence of SEQ ID NO:17 can be modified at residues 1589 and 1775 to form a null mutant, SEQ ID NO:18 can be modified at S1755 to form a null mutant. Similarly, nonphosphorylatable mutants of $InsP_3R$-2 can be formed by substituting alanine for any one or more of the residues 766, 1772, 1856, 2058, 2227 of a wild–type $InsP_3R$-2 sequence or any combination thereof. Nonphosphorylatable mutants of $InsP_3R$-3 can be formed by substituting alanine for any one or more of the residues 934, 1640, 1834, 2009, 2041, 2189 of a wild–type $InsP_3R$-3 sequence or any combination thereof. Similar mutants in various species can be derived by aligning the sequence with the rat sequence provided herein and making the null-inducing substitutions provided herein in the corresponding serine residue.

51. As discussed herein there are numerous variants of the $InsP_3R$ protein that are known and herein contemplated. In addition, to the known functional $InsP_3R$ strain variants, there are derivatives and fragments of the $InsP_3R$ proteins that also function in the disclosed methods and compositions. Protein variants and derivatives are well understood to those of skill in the art and can involve amino acid sequence modifications. For example, amino acid sequence modifications typically fall into one or more of three classes: substitutional, insertional or deletional variants. Insertions include amino and/or carboxyl terminal fusions as well as intrasequence insertions of single or multiple amino acid residues. Insertions ordinarily will be smaller insertions than those of amino or carboxyl terminal fusions, for example, on the order of one to four residues. Immunogenic fusion protein derivatives, such as those described in the examples, are made by fusing a polypeptide sufficiently large to confer immunogenicity to the target sequence by cross-linking *in vitro* or by recombinant cell culture transformed with DNA encoding the fusion. Deletions are characterized by the removal of one or more amino acid residues from the protein sequence. Typically, no more than about from 2 to 6 residues are deleted at any one site within the protein molecule. These variants ordinarily are prepared by site specific mutagenesis of nucleotides in the DNA encoding the protein, thereby producing DNA encoding the variant, and thereafter expressing the DNA in recombinant cell culture. Techniques for making substitution mutations at predetermined sites in DNA having a known sequence are well known, for example M13 primer mutagenesis and PCR mutagenesis. Amino acid substitutions are typically of single residues, but can occur at a number of different locations at once; insertions usually will be on the order of about from 1

to 10 amino acid residues; and deletions will range about from 1 to 30 residues. Deletions or insertions preferably are made in adjacent pairs, i.e. a deletion of 2 residues or insertion of 2 residues. Substitutions, deletions, insertions or any combination thereof may be combined to arrive at a final construct. The mutations must not place the sequence out of reading frame and preferably will not create complementary regions that could produce secondary mRNA structure. Substitutional variants are those in which at least one residue has been removed and a different residue inserted in its place. Such substitutions generally are made in accordance with the following Table 1 and are referred to as conservative substitutions.

TABLE 1:Amino Acid Substitutions

Original Residue	Exemplary Conservative Substitutions, others are known in the art.
Ala	Ser
Arg	Lys; Gln
Asn	Gln; His
Asp	Glu
Cys	Ser
Gln	Asn, Lys
Glu	Asp
Gly	Pro
His	Asn; Gln
Ile	Leu; Val
Leu	Ile; Val
Lys	Arg; Gln;
Met	Leu; Ile
Phe	Met; Leu; Tyr
Ser	Thr
Thr	Ser
Trp	Tyr
Tyr	Trp; Phe
Val	Ile; Leu

52. Substantial changes in function or immunological identity are made by selecting substitutions that are less conservative than those in Table 1, i.e., selecting residues that differ more significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site or (c) the bulk of the side chain. The substitutions which in general are expected to produce the greatest changes in the protein properties will be those in which (a) a hydrophilic residue, e.g. seryl or threonyl, is substituted for (or by) a hydrophobic residue, e.g. leucyl, isoleucyl, phenylalanyl, valyl or alanyl; (b) a cysteine or proline is substituted for (or by) any other residue; (c) a residue having an electropositive side chain, e.g., lysyl, arginyl, or histidyl, is substituted for (or by)

an electronegative residue, e.g., glutamyl or aspartyl; or (d) a residue having a bulky side chain, e.g., phenylalanine, is substituted for (or by) one not having a side chain, e.g., glycine, in this case, (e) by increasing the number of sites for sulfation and/or glycosylation.

53. For example, the replacement of one amino acid residue with another that is biologically and/or chemically similar is known to those skilled in the art as a conservative substitution. For example, a conservative substitution would be replacing one hydrophobic residue for another, or one polar residue for another. The substitutions include combinations such as, for example, Gly, Ala; Val, Ile, Leu; Asp, Glu; Asn, Gln; Ser, Thr; Lys, Arg; and Phe, Tyr. Such conservatively substituted variations of each explicitly disclosed sequence are included within the mosaic polypeptides provided herein.

54. Substitutional or deletional mutagenesis can be employed to insert sites for N-glycosylation (Asn-X-Thr/Ser) or O-glycosylation (Ser or Thr). Deletions of cysteine or other labile residues also may be desirable. Deletions or substitutions of potential proteolysis sites, e.g. Arg, is accomplished for example by deleting one of the basic residues or substituting one by glutaminyl or histidyl residues.

55. Certain post-translational derivatizations are the result of the action of recombinant host cells on the expressed polypeptide. Glutaminyl and asparaginyl residues are frequently post-translationally deamidated to the corresponding glutamyl and asparyl residues. Alternatively, these residues are deamidated under mildly acidic conditions. Other post-translational modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the o-amino groups of lysine, arginine, and histidine side chains (T.E. Creighton, Proteins: Structure and Molecular Properties, W. H. Freeman & Co., San Francisco pp 79-86 [1983]), acetylation of the N-terminal amine and, in some instances, amidation of the C-terminal carboxyl.

56. It is understood that one way to define the variants and derivatives of the disclosed proteins herein is through defining the variants and derivatives in terms of homology/identity to specific known sequences. For example, SEQ ID NO: 1 sets forth a particular sequence of the "short form" ($S2^-$) of $InsP_3R$-1 (short form S1589E) and SEQ ID NO: 2 sets forth a particular sequence of the "long form" ($S2^+$) of $InsP_3R$-1 protein (long form S1589E). Specifically disclosed are variants of these and other proteins herein disclosed which have at least, 70% or 75% or 80% or 85% or 90% or 95% homology to the stated sequence. Those of skill in the art readily understand how to determine the homology of two proteins.

57. It is understood that the description of conservative mutations and homology can be combined together in any combination, such as embodiments that have at least 70% homology to a particular sequence wherein the variants are conservative mutations.

58. As this specification discusses various proteins and protein sequences it is understood that the nucleic acids that can encode those protein sequences are also disclosed. This would include all degenerate sequences related to a specific protein sequence, i.e. all nucleic acids having a sequence that encodes one particular protein sequence as well as all nucleic acids, including degenerate nucleic acids, encoding the disclosed variants and derivatives of the protein sequences. Thus, while each particular nucleic acid sequence may not be written out herein, it is understood that each and every sequence is in fact disclosed and described herein through the disclosed protein sequence. For example, one of the many nucleic acid sequences that can encode the protein sequence set forth in SEQ ID NO: 18 is set forth in SEQ ID NO: 22. In addition, for example, a disclosed conservative derivative of SEQ ID NO: 1 is shown in SEQ ID NO: 3, where the isoleucine (E) at position 1589 is changed to a valine (D). It is understood that for this mutation all of the nucleic acid sequences that encode this particular derivative of the short form S1589E are also disclosed. It is also understood that while no amino acid sequence indicates what particular DNA sequence encodes that protein within an organism, where particular variants of a disclosed protein are disclosed herein, the known nucleic acid sequence that encodes that protein is also known and herein disclosed and described.

59. Also provided are fragments of the proteins described below, wherein the fragments maintain the Ca^{2+} enhancing or reducing function of full length protein. Preferably the fragment will have at least 50% of the enhancing function of the full length correlate or at least a 50% reduction of the Ca^{2+} reducing function.

Nucleic Acids, Vectors and Expression Systems

60. The invention further provides nucleic acids that encode the mutants described herein. Examples of nucleic acids that encode the $InsP_3R$-1 wild type receptors can be found at http://www.ncbi.nlm.nih.gov/HomoloGene/homol.cgi?HID=30927, including for example rat (ATCC Acc. No. xm_342732); mouse (ATCC Acc. No. nm_010585); human (ATCC Acc. No. nm_002222). Examples of nucleic acids that encode the $InsP_3R$-2 wild-type receptors can also be found at the http://www.ncbi.nlm.nih.gov site and include, for example, rat (ATCC Acc. No. NM_031046), human (ATCC Acc. No. NM_002223). Examples of nucleic acids that encode the $InsP_3R$-3 wild-type receptors can also be found at

the http://www.ncbi.nlm.nih.gov site and include, for example, rat (ATCC Acc. No. NM_013138), human (ATCC Acc. No. NM_002224), and mouse (ATCC Acc. No. NM_080553).

61. One of skill in the art could modify these nucleic acid sequences to make the substitutions described herein. For example, the codon for the selected serine is replaced by a codon for glutamate, aspartate, or alanine. Further provided are nucleic acids that comprise a sequence that hybridizes under highly stringent conditions to the various rat, mouse, and human mutatnts encoding nucleic acids with the selected serine(s) substituted with glutamate, aspartate, or alanine. Preferably these hybridizing nucleic acids do not hybridize to the wild-type encoding nucleic acids.

62. The term hybridization typically means a sequence driven interaction between at least two nucleic acid molecules, such as a primer or a probe and a gene. Sequence driven interaction means an interaction that occurs between two nucleotides or nucleotide analogs or nucleotide derivatives in a nucleotide specific manner. For example, G interacting with C or A interacting with T are sequence driven interactions. Typically sequence driven interactions occur on the Watson-Crick face or Hoogsteen face of the nucleotide. The hybridization of two nucleic acids is affected by a number of conditions and parameters known to those of skill in the art. For example, the salt concentrations, pH, and temperature of the reaction all affect whether two nucleic acid molecules will hybridize.

63. Parameters for selective hybridization between two nucleic acid molecules are well known to those of skill in the art. For example, in some embodiments selective hybridization conditions can be defined as stringent or highly stringent hybridization conditions. For example, stringency of hybridization is controlled by both temperature and salt concentration of either or both of the hybridization and washing steps. For example, the conditions of hybridization to achieve selective hybridization may involve hybridization in high ionic strength solution (6X SSC or 6X SSPE) at a temperature that is about 12-25°C below the Tm (the melting temperature at which half of the molecules dissociate from their hybridization partners) followed by washing at a combination of temperature and salt concentration chosen so that the washing temperature is about 5°C to 20°C below the Tm. The temperature and salt conditions are readily determined empirically in preliminary experiments in which samples of reference DNA immobilized on filters are hybridized to a labeled nucleic acid of interest and then washed under conditions of different stringencies. Hybridization temperatures are typically higher for DNA-RNA and RNA-RNA hybridizations. The conditions can be used as described above to achieve stringency, or as

is known in the art. (Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1989; Kunkel et al. Methods Enzymol. 1987:154:367, 1987 which is herein incorporated by reference for material at least related to hybridization of nucleic acids). A preferable stringent hybridization condition for a DNA:DNA hybridization can be at about 68°C (in aqueous solution) in 6X SSC or 6X SSPE followed by washing at 68°C. Stringency of hybridization and washing, if desired, can be reduced accordingly as the degree of complementarity desired is decreased, and further, depending upon the G-C or A-T richness of any area wherein variability is searched for. Likewise, stringency of hybridization and washing, if desired, can be increased accordingly as homology desired is increased, and further, depending upon the G-C or A-T richness of any area wherein high homology is desired, all as known in the art.

64. Another way to define selective hybridization is by looking at the amount (percentage) of one of the nucleic acids bound to the other nucleic acid. For example, in some embodiments selective hybridization conditions would be when at least about, 60, 65, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 percent of the limiting nucleic acid is bound to the non-limiting nucleic acid. Typically, the non-limiting primer is in for example, 10 or 100 or 1000 fold excess. This type of assay can be performed at under conditions where both the limiting and non-limiting primer are for example, 10 fold or 100 fold or 1000 fold below their k_d, or where only one of the nucleic acid molecules is 10 fold or 100 fold or 1000 fold or where one or both nucleic acid molecules are above their k_d.

65. Another way to define selective hybridization is by looking at the percentage of primer that gets enzymatically manipulated under conditions where hybridization is required to promote the desired enzymatic manipulation. For example, in some embodiments selective hybridization conditions would be when at least about, 60, 65, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 percent of the primer is enzymatically manipulated under conditions which promote the enzymatic manipulation, for example if the enzymatic manipulation is DNA extension, then selective hybridization conditions would be when at least about 60, 65, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 percent of the primer molecules are extended. Preferred conditions also include those suggested by the manufacturer or indicated in the art as being appropriate for the enzyme performing the manipulation.

66. Just as with homology, it is understood that there are a variety of methods herein disclosed for determining the level of hybridization between two nucleic acid molecules. It is understood that these methods and conditions may provide different percentages of hybridization between two nucleic acid molecules, but unless otherwise indicated meeting the parameters of any of the methods would be sufficient. For example if 80% hybridization was required and as long as hybridization occurs within the required parameters in any one of these methods it is considered disclosed herein.

67. It is understood that those of skill in the art understand that if a composition or method meets any one of these criteria for determining hybridization either collectively or singly it is a composition or method that is disclosed herein.

68. Also provided are fragments of at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 nucleotides (or any number in between) of the nucleic acids provided herein, wherein the fragment encodes a serine substitution described herein.

69. The invention also provides an expression vector comprising a nucleic acid of the invention wherein the nucleic acid is operable linked to an expression control sequence.

70. The nucleic acids that are delivered to cells typically contain expression controlling systems. For example, the inserted genes in viral and retroviral systems usually contain promoters, and/or enhancers to help control the expression of the desired gene product. A promoter is generally a sequence or sequences of DNA that function when in a relatively fixed location in regard to the transcription start site. A promoter contains core elements required for basic interaction of RNA polymerase and transcription factors, and may contain upstream elements and response elements.

71. There are a number of compositions and methods which can be used to deliver nucleic acids to cells, either *in vitro* or *in vivo*. These methods and compositions can largely be broken down into two classes: viral based delivery systems and non-viral based delivery systems. For example, the nucleic acids can be delivered through a number of direct delivery systems such as, electroporation, lipofection, calcium phosphate precipitation, plasmids, viral vectors, viral nucleic acids, phage nucleic acids, phages, cosmids, or via transfer of genetic material in cells or carriers such as cationic liposomes. Appropriate means for transfection, including viral vectors, chemical transfectants, or physico-mechanical methods such as electroporation and direct diffusion of DNA, are described by, for example, Wolff, J. A., et al., *Science*, 247, 1465-1468, (1990); and Wolff, J. A. *Nature*, 352, 815-818, (1991). Such methods are well known in the art and readily adaptable for use with the compositions and methods described herein. In certain cases, the methods will be

modifed to specifically function with large DNA molecules. Further, these methods can be used to target certain diseases and cell populations by using the targeting characteristics of the carrier.

72. Transfer vectors can be any nucleotide construction used to deliver genes into cells (e.g., a plasmid), or as part of a general strategy to deliver genes, e.g., as part of recombinant retrovirus or adenovirus (Ram et al. Cancer Res. 53:83-88, (1993)).

73. As used herein, plasmid or viral vectors are agents that transport the disclosed nucleic acids, such as SEQ ID NO: 22 into the cell without degradation and include a promoter yielding expression of the gene in the cells into which it is delivered. Viral vectors are, for example, Adenovirus, Adeno-associated virus, Herpes virus, Vaccinia virus, Polio virus, AIDS virus, neuronal trophic virus, Sindbis and other RNA viruses, including these viruses with the HIV backbone. Also preferred are any viral families which share the properties of these viruses which make them suitable for use as vectors. Retroviruses include Murine Maloney Leukemia virus, MMLV, and retroviruses that express the desirable properties of MMLV as a vector. Retroviral vectors are able to carry a larger genetic payload, i.e., a transgene or marker gene, than other viral vectors, and for this reason are a commonly used vector. However, they are not as useful in non-proliferating cells. Adenovirus vectors are relatively stable and easy to work with, have high titers, and can be delivered in aerosol formulation, and can transfect non-dividing cells. Pox viral vectors are large and have several sites for inserting genes, they are thermostable and can be stored at room temperature. A preferred embodiment is a viral vector which has been engineered so as to suppress the immune response of the host organism, elicited by the viral antigens. Preferred vectors of this type will carry coding regions for Interleukin 8 or 10.

74. Viral vectors can have higher transaction (ability to introduce genes) abilities than chemical or physical methods to introduce genes into cells. Typically, viral vectors contain, nonstructural early genes, structural late genes, an RNA polymerase III transcript, inverted terminal repeats necessary for replication and encapsidation, and promoters to control the transcription and replication of the viral genome. When engineered as vectors, viruses typically have one or more of the early genes removed and a gene or gene/promotor cassette is inserted into the viral genome in place of the removed viral DNA. Constructs of this type can carry up to about 8 kb of foreign genetic material. The necessary functions of the removed early genes are typically supplied by cell lines which have been engineered to express the gene products of the early genes in trans.

75. A retrovirus is an animal virus belonging to the virus family of Retroviridae, including any types, subfamilies, genus, or tropisms. Retroviral vectors, in general, are described by Verma, I.M., Retroviral vectors for gene transfer. In Microbiology-1985, American Society for Microbiology, pp. 229-232, Washington, (1985), which is incorporated by reference herein. Examples of methods for using retroviral vectors for gene therapy are described in U.S. Patent Nos. 4,868,116 and 4,980,286; PCT applications WO 90/02806 and WO 89/07136; and Mulligan, (Science 260:926-932 (1993)); the teachings of which are incorporated herein by reference.

76. A retrovirus is essentially a package which has packed into it nucleic acid cargo. The nucleic acid cargo carries with it a packaging signal, which ensures that the replicated daughter molecules will be efficiently packaged within the package coat. In addition to the package signal, there are a number of molecules which are needed in cis, for the replication, and packaging of the replicated virus. Typically a retroviral genome, contains the gag, pol, and env genes which are involved in the making of the protein coat. It is the gag, pol, and env genes which are typically replaced by the foreign DNA that it is to be transferred to the target cell. Retrovirus vectors typically contain a packaging signal for incorporation into the package coat, a sequence which signals the start of the gag transcription unit, elements necessary for reverse transcription, including a primer binding site to bind the tRNA primer of reverse transcription, terminal repeat sequences that guide the switch of RNA strands during DNA synthesis, a purine rich sequence 5' to the 3' LTR that serve as the priming site for the synthesis of the second strand of DNA synthesis, and specific sequences near the ends of the LTRs that enable the insertion of the DNA state of the retrovirus to insert into the host genome. The removal of the gag, pol, and env genes allows for about 8 kb of foreign sequence to be inserted into the viral genome, become reverse transcribed, and upon replication be packaged into a new retroviral particle. This amount of nucleic acid is sufficient for the delivery of a one to many genes depending on the size of each transcript. It is preferable to include either positive or negative selectable markers along with other genes in the insert.

77. Since the replication machinery and packaging proteins in most retroviral vectors have been removed (gag, pol, and env), the vectors are typically generated by placing them into a packaging cell line. A packaging cell line is a cell line which has been transfected or transformed with a retrovirus that contains the replication and packaging machinery, but lacks any packaging signal. When the vector carrying the DNA of choice is transfected into these cell lines, the vector containing the gene of interest is replicated and packaged into

new retroviral particles, by the machinery provided in cis by the helper cell. The genomes for the machinery are not packaged because they lack the necessary signals.

78. The construction of replication-defective adenoviruses has been described (Berkner et al., *J. Virology* 61:1213-1220 (1987); Massie et al., Mol. Cell. Biol. 6:2872-2883 (1986); Haj-Ahmad et al., *J. Virology* 57:267-274 (1986); Davidson et al., *J. Virology* 61:1226-1239 (1987); Zhang, *BioTechniques* 15:868-872 (1993)). The benefit of the use of these viruses as vectors is that they are limited in the extent to which they can spread to other cell types, since they can replicate within an initial infected cell, but are unable to form new infectious viral particles. Recombinant adenoviruses have been shown to achieve high efficiency gene transfer after direct, *in vivo* delivery to airway epithelium, hepatocytes, vascular endothelium, CNS parenchyma and a number of other tissue sites (Morsy, *J. Clin. Invest.* 92:1580-1586 (1993); Kirshenbaum, *J. Clin. Invest.* 92:381-387 (1993); Roessler, *J. Clin. Invest.* 92:1085-1092 (1993); Moullier, *Nature Genetics* 4:154-159 (1993); La Salle, *Science* 259:988-990 (1993); Gomez-Foix, *J. Biol. Chem.* 267:25129-25134 (1992); Rich, *Human Gene Therapy* 4:461-476 (1993); Zabner, *Nature Genetics* 6:75-83 (1994); Guzman, *Circulation Research* 73:1201-1207 (1993); Bout, *Human Gene Therapy* 5:3-10 (1994); Zabner, *Cell* 75:207-216 (1993); Caillaud, *Eur. J. Neuroscience* 5:1287-1291 (1993); and Ragot, *J. Gen. Virology* 74:501-507 (1993)). Recombinant adenoviruses achieve gene transduction by binding to specific cell surface receptors, after which the virus is internalized by receptor-mediated endocytosis, in the same manner as wild type or replication-defective adenovirus (Chardonnet and Dales, *Virology* 40:462-477 (1970); Brown and Burlingham, *J. Virology* 12:386-396 (1973); Svensson and Persson, *J. Virology* 55:442-449 (1985); Seth, et al., *J. Virol.* 51:650-655 (1984); Seth, et al., *Mol. Cell. Biol.* 4:1528-1533 (1984); Varga et al., *J. Virology* 65:6061-6070 (1991); Wickham et al., *Cell* 73:309-319 (1993)).

79. A viral vector can be one based on an adenovirus which has had the E1 gene removed and these virons are generated in a cell line such as the human 293 cell line. In another preferred embodiment both the E1 and E3 genes are removed from the adenovirus genome.

80. Another type of viral vector is based on an adeno-associated virus (AAV). This defective parvovirus is a preferred vector because it can infect many cell types and is nonpathogenic to humans. AAV type vectors can transport about 4 to 5 kb and wild type AAV is known to stably insert into chromosome 19. Vectors which contain this site specific integration property are preferred. An especially preferred embodiment of this type

of vector is the P4.1 C vector produced by Avigen, San Francisco, CA, which can contain the herpes simplex virus thymidine kinase gene, HSV-tk, and/or a marker gene, such as the gene encoding the green fluorescent protein, GFP.

81. In another type of AAV virus, the AAV contains a pair of inverted terminal repeats (ITRs) which flank at least one cassette containing a promoter which directs cell-specific expression operably linked to a heterologous gene. Heterologous in this context refers to any nucleotide sequence or gene which is not native to the AAV or B19 parvovirus.

82. Typically the AAV and B19 coding regions have been deleted, resulting in a safe, noncytotoxic vector. The AAV ITRs, or modifications thereof, confer infectivity and site-specific integration, but not cytotoxicity, and the promoter directs cell-specific expression. United States Patent No. 6,261,834 is herein incorproated by reference for material related to the AAV vector.

83. The vectors of the present invention thus provide DNA molecules which are capable of integration into a mammalian chromosome without substantial toxicity.

84. The inserted genes in viral and retroviral usually contain promoters, and/or enhancers to help control the expression of the desired gene product. A promoter is generally a sequence or sequences of DNA that function when in a relatively fixed location in regard to the transcription start site. A promoter contains core elements required for basic interaction of RNA polymerase and transcription factors, and may contain upstream elements and response elements.

85. Molecular genetic experiments with large human herpesviruses have provided a means whereby large heterologous DNA fragments can be cloned, propagated and established in cells permissive for infection with herpesviruses (Sun et al., *Nature Genetics* 8: 33-41, 1994; Cotter and Robertson,.*Curr Opin Mol Ther* 5: 633-644, 1999). These large DNA viruses (herpes simplex virus (HSV) and Epstein-Barr virus (EBV), have the potential to deliver fragments of human heterologous DNA > 150 kb to specific cells. EBV recombinants can maintain large pieces of DNA in the infected B-cells as episomal DNA. Individual clones carried human genomic inserts up to 330 kb appeared genetically stable The maintenance of these episomes requires a specific EBV nuclear protein, EBNA1, constitutively expressed during infection with EBV. Additionally, these vectors can be used for transfection, where large amounts of protein can be generated transiently *in vitro*. Herpesvirus amplicon systems are also being used to package pieces of DNA > 220 kb and to infect cells that can stably maintain DNA as episomes.

86. Other useful systems include, for example, replicating and host-restricted non-replicating vaccinia virus vectors.

87. The disclosed compositions can be delivered to the target cells in a variety of ways. For example, the compositions can be delivered through use of a gene gun, electroporation, or through lipofection, or through calcium phosphate precipitation. The delivery mechanism chosen will depend in part on the type of cell targeted and whether the delivery is occurring for example *in vivo* or *in vitro*.

88. Thus, the compositions can comprise, in addition to the disclosed vectors for example, lipids such as liposomes (cationic liposomes (e.g., DOTMA, DOPE, DC-cholesterol) or anionic liposomes). Liposomes can further comprise proteins to facilitate targeting a particular cell, if desired. Administration of a composition comprising a compound and a cationic liposome can be administered to the blood afferent to a target organ or inhaled into the respiratory tract to target cells of the respiratory tract. Regarding liposomes, see, e.g., Brigham et al. *Am. J. Resp. Cell. Mol. Biol.* 1:95-100 (1989); Felgner et al. *Proc. Natl. Acad. Sci USA* 84:7413-7417 (1987); U.S. Pat. No.4,897,355. Furthermore, the compound can be administered as a component of a microcapsule that can be targeted to specific cell types, such as macrophages, or where the diffusion of the compound or delivery of the compound from the microcapsule is designed for a specific rate or dosage.

89. In the methods described above which include the administration and uptake of exogenous DNA into the cells of a subject (i.e., gene transduction or transfection), delivery of the compositions to cells can be via a variety of mechanisms. As one example, delivery can be via a liposome, using commercially available liposome preparations such as LIPOFECTIN, LIPOFECTAMINE (GIBCO-BRL, Inc., Gaithersburg, MD), SUPERFECT (Qiagen, Inc. Hilden, Germany) and TRANSFECTAM (Promega Biotec, Inc., Madison, WI), as well as other liposomes developed according to procedures standard in the art. In addition, the nucleic acid or vector of this invention can be delivered *in vivo* by electroporation, the technology for which is available from Genetronics, Inc. (San Diego, CA) as well as by means of a SONOPORATION machine (ImaRx Pharmaceutical Corp., Tucson, AZ).

90. The materials may be in solution, suspension (for example, incorporated into microparticles, liposomes, or cells). These may be targeted to a particular cell type via antibodies, receptors, or receptor ligands. The following references are examples of the use of this technology to target specific proteins to tumor tissue (Senter, et al., *Bioconjugate Chem.*, 2:447-451, (1991); Bagshawe, K.D., *Br. J. Cancer*, 60:275-281, (1989); Bagshawe,

et al., *Br. J. Cancer*, 58:700-703, (1988); Senter, et al., *Bioconjugate Chem.*, 4:3-9, (1993); Battelli, et al., *Cancer Immunol. Immunother.*, 35:421-425, (1992); Pietersz and McKenzie, *Immunolog. Reviews*, 129:57-80, (1992); and Roffler, et al., *Biochem. Pharmacol*, 42:2062-2065, (1991)). These techniques can be used for a variety of other speciifc cell types. Vehicles such as "stealth" and other antibody conjugated liposomes (including lipid mediated drug targeting to colonic carcinoma), receptor mediated targeting of DNA through cell specific ligands, lymphocyte directed tumor targeting, and highly specific therapeutic retroviral targeting of murine glioma cells *in vivo*. The following references are examples of the use of this technology to target specific proteins to tumor tissue (Hughes et al., *Cancer Research*, 49:6214-6220, (1989); and Litzinger and Huang, *Biochimica et Biophysica Acta*, 1104:179-187, (1992)). In general, receptors are involved in pathways of endocytosis, either constitutive or ligand induced. These receptors cluster in clathrin-coated pits, enter the cell via clathrin-coated vesicles, pass through an acidified endosome in which the receptors are sorted, and then either recycle to the cell surface, become stored intracellularly, or are degraded in lysosomes. The internalization pathways serve a variety of functions, such as nutrient uptake, removal of activated proteins, clearance of macromolecules, opportunistic entry of viruses and toxins, dissociation and degradation of ligand, and receptor-level regulation. Many receptors follow more than one intracellular pathway, depending on the cell type, receptor concentration, type of ligand, ligand valency, and ligand concentration. Molecular and cellular mechanisms of receptor-mediated endocytosis has been reviewed (Brown and Greene, *DNA and Cell Biology* 10:6, 399-409 (1991)).

91. Nucleic acids that are delivered to cells which are to be integrated into the host cell genome, typically contain integration sequences. These sequences are often viral related sequences, particularly when viral based systems are used. These viral intergration systems can also be incorporated into nucleic acids which are to be delivered using a non-nucleic acid based system of deliver, such as a liposome, so that the nucleic acid contained in the delivery system can be come integrated into the host genome.

92. Other general techniques for integration into the host genome include, for example, systems designed to promote homologous recombination with the host genome. These systems typically rely on sequence flanking the nucleic acid to be expressed that has enough homology with a target sequence within the host cell genome that recombination between the vector nucleic acid and the target nucleic acid takes place, causing the delivered nucleic

acid to be integrated into the host genome. These systems and the methods necessary to promote homologous recombination are known to those of skill in the art.

93. As described above, the compositions can be administered in a pharmaceutically acceptable carrier and can be delivered to the subject's cells *in vivo* and/or *ex vivo* by a variety of mechanisms well known in the art (e.g., uptake of naked DNA, liposome fusion, intramuscular injection of DNA via a gene gun, endocytosis and the like).

94. If *ex vivo* methods are employed, cells or tissues can be removed and maintained outside the body according to standard protocols well known in the art. The compositions can be introduced into the cells via any gene transfer mechanism, such as, for example, calcium phosphate mediated gene delivery, electroporation, microinjection or proteoliposomes. The transduced cells can then be infused (e.g., in a pharmaceutically acceptable carrier) or homotopically transplanted back into the subject per standard methods for the cell or tissue type. Standard methods are known for transplantation or infusion of various cells into a subject.

95. The invention also provides a cell comprising a vector described herein. Preferably the cultured cell, in the absence of the vector does not express $InsP_3Rs$. Optionally, the cell is a cultured cell. An example of such a cell is the DT-40 3ko cell. Optionally, the cell further comprises a nucleic acid that encodes an acetylcholine receptor (including for example an M3 receptor). Optionally various labels can be used to identify the cells that are successfully transfected or transformed.

96. Preferred promoters controlling transcription from vectors in mammalian host cells may be obtained from various sources, for example, the genomes of viruses such as: polyoma, Simian Virus 40 (SV40), adenovirus, retroviruses, hepatitis-B virus and most preferably cytomegalovirus, or from heterologous mammalian promoters, e.g. beta actin promoter. The early and late promoters of the SV40 virus are conveniently obtained as an SV40 restriction fragment which also contains the SV40 viral origin of replication (Fiers et al., *Nature*, 273: 113 (1978)). The immediate early promoter of the human cytomegalovirus is conveniently obtained as a *Hin*dIII E restriction fragment (Greenway, P.J. et al., *Gene* 18: 355-360 (1982)). Of course, promoters from the host cell or related species also are useful herein.

97. Enhancer generally refers to a sequence of DNA that functions at no fixed distance from the transcription start site and can be either 5' (Laimins, L. et al., *Proc. Natl. Acad. Sci.* 78: 993 (1981)) or 3' (Lusky, M.L., et al., *Mol. Cell Bio.* 3: 1108 (1983)) to the transcription unit. Furthermore, enhancers can be within an intron (Banerji, J.L. et al., *Cell*

33: 729 (1983)) as well as within the coding sequence itself (Osborne, T.F., et al., *Mol. Cell Bio.* 4: 1293 (1984)). They are usually between 10 and 300 bp in length, and they function in cis. Enhancers function to increase transcription from nearby promoters. Enhancers also often contain response elements that mediate the regulation of transcription. Promoters can also contain response elements that mediate the regulation of transcription. Enhancers often determine the regulation of expression of a gene. While many enhancer sequences are now known from mammalian genes (globin, elastase, albumin, -fetoprotein and insulin), typically one will use an enhancer from a eukaryotic cell virus for general expression. Preferred examples are the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers.

98. The promotor and/or enhancer may be specifically activated either by light or specific chemical events which trigger their function. Systems can be regulated by reagents such as tetracycline and dexamethasone. There are also ways to enhance viral vector gene expression by exposure to irradiation, such as gamma irradiation, or alkylating chemotherapy drugs.

99. In certain embodiments the promoter and/or enhancer region can act as a constitutive promoter and/or enhancer to maximize expression of the region of the transcription unit to be transcribed. In certain constructs the promoter and/or enhancer region be active in all eukaryotic cell types, even if it is only expressed in a particular type of cell at a particular time. A preferred promoter of this type is the CMV promoter (650 bases). Other preferred promoters are SV40 promoters, cytomegalovirus (full length promoter), and retroviral vector LTF.

100. It has been shown that all specific regulatory elements can be cloned and used to construct expression vectors that are selectively expressed in specific cell types such as melanoma cells. The glial fibrillary acetic protein (GFAP) promoter has been used to selectively express genes in cells of glial origin.

101. Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human or nucleated cells) may also contain sequences necessary for the termination of transcription which may affect mRNA expression. These regions are transcribed as polyadenylated segments in the untranslated portion of the mRNA encoding tissue factor protein. The 3' untranslated regions also include transcription termination sites. It is preferred that the transcription unit also contain a polyadenylation region. One benefit of this region is that it increases the likelihood that the transcribed unit will be processed and

transported like mRNA. The identification and use of polyadenylation signals in expression constructs is well established. It is preferred that homologous polyadenylation signals be used in the transgene constructs. In certain transcription units, the polyadenylation region is derived from the SV40 early polyadenylation signal and consists of about 400 bases. It is also preferred that the transcribed units contain other standard sequences alone or in combination with the above sequences improve expression from, or stability of, the construct.

102. The viral vectors can include nucleic acid sequence encoding a marker product. This marker product is used to determine if the gene has been delivered to the cell and once delivered is being expressed. Preferred marker genes are the *E. Coli* lacZ gene, which encodes ß-galactosidase, and green fluorescent protein.

103. In some embodiments the marker may be a selectable marker. Examples of suitable selectable markers for mammalian cells are dihydrofolate reductase (DHFR), thymidine kinase, neomycin, neomycin analog G418, hydromycin, and puromycin. When such selectable markers are successfully transferred into a mammalian host cell, the transformed mammalian host cell can survive if placed under selective pressure. There are two widely used distinct categories of selective regimes. The first category is based on a cell's metabolism and the use of a mutant cell line which lacks the ability to grow independent of a supplemented media. Two examples are: CHO DHFR- cells and mouse LTK- cells. These cells lack the ability to grow without the addition of such nutrients as thymidine or hypoxanthine. Because these cells lack certain genes necessary for a complete nucleotide synthesis pathway, they cannot survive unless the missing nucleotides are provided in a supplemented media. An alternative to supplementing the media is to introduce an intact DHFR or TK gene into cells lacking the respective genes, thus altering their growth requirements. Individual cells which were not transformed with the DHFR or TK gene will not be capable of survival in non-supplemented media.

104. The second category is dominant selection which refers to a selection scheme used in any cell type and does not require the use of a mutant cell line. These schemes typically use a drug to arrest growth of a host cell. Those cells which have a novel gene would express a protein conveying drug resistance and would survive the selection. Examples of such dominant selection use the drugs neomycin, (Southern P. and Berg, P., *J. Molec. Appl. Genet.* 1: 327 (1982)), mycophenolic acid, (Mulligan, R.C. and Berg, P. *Science* 209: 1422 (1980)) or hygromycin, (Sugden, B. et al., *Mol. Cell. Biol.* 5: 410-413 (1985)). The three examples employ bacterial genes under eukaryotic control to convey resistance to the

appropriate drug G418 or neomycin (geneticin), xgpt (mycophenolic acid) or hygromycin, respectively. Others include the neomycin analog G418 and puramycin.

105. The invention further provides methods of using the mutants, nucleic acids, and cells of the invention in various methods of making the mutant receptors, methods of screening for agents that modulate the $InsP_3Rs$, and methods of treatment.

106. The expression systems described herein can be used to make mutant $InsP_3Rs$. Thus, the invention provides making mutant $InsP_3R$-1, $InsP_3R$-2, $InsP_3R$-3 or fragments thereof described herein by culturing a cell that expresses the selected mutant or fragments under conditions that allow expression and by isolating the expressed mutant or fragment thereof.

107. The invention further provides a method of screening for an agent that preferentially modulates Ca^{2+} release by phosphorylated $InsP_3R$, comprising contacting a cell of the invention with the agent to be screened, under conditions that allow Ca^{2+} release; measuring Ca^{2+} release; and comparing the amount of Ca^{2+} release with a control cell. The control cell can comprise an unphosphorylated $InsP_3R$ that is not contacted with the agent to be screened. Conditions that allow calcium release include for example carbachol, acting at muscaric M3 receptors or alternatively, an agonist acting at any one of over one hundered plasma membrane receptors for neurotransmitters, hormones and growth factors coupled to the formation of $InsP_3$. In addition, ehanced Ca^{2+} release can occur following direct activation of $InsP_3R$ with $InsP_3$ or its analogs. An increase or decrease in Ca^{2+} release as compared to a control cell indicates an agent that preferentially modulates unphosphorylated $InsP_3R$. By "modulation" is meant any physiologic effect that increases or decreases $InsP_3R$ stimulated calcium release. Preferably the unphosphorylated $InsP_3R$ is a nonphosphorylatable mutant $InsP_3R$ described herein.

108. The invention also provides a method of expressing a mutant InsP3R in a cell *in vivo*, comprising providing an expression vector described herein; introducing the vector into a cell *in vivo*; maintaining the cell under conditions that permit expression of the mutant $InsP_3R$ by the cell.

109. Also provided herein are methods of treating a subject with reduced Ca^{2+} release, comprising introducing into the subject an expression vector that encodes a phosphomimetic mutant of the invention, under conditions that an amount of the mutant receptor is expressed in an effective amount to enhance Ca^{2+} release. Examples of such diseases include, xerostomia, cystic fibrosis, or a large class of diseases which result from the decreased secretion of hormones, these include but are not limited to, decreased thyroid stimulating

hormone (TSH) secretion from the pituitary or insulin secretion from the pancreas. The former deficiency results in dwarfism and cretinism, the latter diabetes.

110. Optionally the expression vector can be targeted. For example, to treat a subject with a condition like xerostomia, the vector could be targeted to the oral mucosal cells.

111. The invention also provides a method of treating a subject with cystic fibrosis, comprising introducing into the subject the expression vector of that expresses a phosphomimetic mutant receptor under conditions that an amount of the mutant receptor is expressed in an effective amount to alleviate the symptoms of cystic fibrosis.

EXAMPLES

Example 1: Phosphorylation of Type-1 Inositol 1,4,5-Trisphosphate Receptors by Cyclic Nucleotide-dependent Protein Kinases

112. Inositol 1,4,5-trisphosphate receptors ($InsP_3R$) constitute the major route of intracellular calcium release in eukaryotic cells and as such are pivotal for stimulation of Ca^{2+} dependent effectors important for numerous physiological processes. Modulation of this release has important consequences for defining the particular spatio-temporal characteristics of Ca^{2+} signals. In this study, regulation of Ca^{2+} release by phosphorylation of type-1 $InsP_3R$ ($InsP_3R$-1) by cAMP (PKA) and cGMP (PKG) dependent protein kinases was investigated in the two major splice variants of $InsP_3R$-1. $InsP_3R$-1 were expressed in DT-40 cells devoid of endogenous $InsP_3R$. In cells expressing the neuronal, $S2^+$ splice variant of the $InsP_3R$-1, Ca^{2+} release was markedly enhanced when either PKA or PKG was activated. The sites of phosphorylation were investigated by mutation of serine residues present in two canonical phosphorylation sites present in the protein. Potentiated Ca^{2+} release was abolished when serine 1755 was mutated to alanine (S1755A) but was unaffected by a similar mutation of serine 1589 (S1589A). These data demonstrate that S1755 is the functionally important residue for phosphoregulation by PKA and PKG in the neuronal variant of the $InsP_3R$-1. Activation of PKA also resulted in potentiated Ca^{2+} release in cells expressing the non-neuronal, $S2^-$ splice variant of the $InsP_3R$-1. However, the PKA-induced potentiation was still evident in S1589A or S1755A $InsP_3R$-1 mutants. The effect was abolished in the double (S1589A/S1755A) mutant, indicating both sites are phosphorylated and contribute to the functional effect. Activation of PKG had no effect on Ca^{2+} release in cells expressing the $S2^-$ variant of $InsP_3R$-1. Collectively these data indicated that phosphoregulation of $InsP_3R$-1 had dramatic effects on Ca^{2+} release and

defined the molecular sites phosphorylated in the major variants expressed in neuronal and peripheral tissues.

113. Most studies of PKA-dependent phosphorylation have been performed on the $S2^+$ neuronal type-I $InsP_3R$, the so called "long-form" of the receptor. In this variant of the $InsP_3R$-1, serine residues at S1589 and S1755 are phosphorylated by PKA [7, 34, 35], with S1755 being more heavily phosphorylated [34]. In contrast, little consensus exists as to the effect of PKG; *in situ* experiments in cerebellar slices reported S1589 to be preferentially phosphorylated by PKG [35] , while other studies suggest that purified $InsP_3R$-1 protein from the cerebellum was phosphorylated preferentially on S1755 [36].

114. Alternative splicing of the type-1 receptor gene results in the $S2^-$ variant of the type-1 $InsP_3R$ where 40 amino acids (amino acids 1693 to 1732) are excised between the two phosphorylation sites [6, 7]. This protein is predominantly expressed in peripheral tissues and interestingly has been reported to be exclusively phosphorylated on S1589 by PKA [7], but on S1755 by PKG [36]. Studies of the functional effects of phosphorylation of the peripheral form have suggested that in contrast to the neuronal form of the receptor, phosphorylation of the "short form" of the $InsP_3R$-1 results in attenuated Ca^{2+} release [21, 22]. Thus, prior to this invention, the possibility existed that differences in both the sites of phosphorylation and therefore the functional effects of phosphorylation were defined by the particular splice variants expressed in particular tissues.

115. In this study the sites of phosphorylation by PKA and PKG, functionally important for regulation of Ca^{2+} release in the two major splice variants of the $InsP_3R$-1, were investigated. By expression of mutant $InsP_3R$-1 in $InsP_3R$ *null* DT-40 cells [42, 43], the studies revealed that phosphorylation of S1755 by PKA or PKG resulted in markedly enhanced Ca^{2+} release for $S2^+$ $InsP_3R$-1. Notably, in $S2^-$ $InsP_3R$ expressing cells PKG activation did not markedly alter Ca^{2+} release while PKA phosphorylation of both S1755 and S1589 result in enhanced Ca^{2+} release. Thus, the expression of particular $InsP_3R$ splice variants defined the functional consequences of phosphoregulation by cyclic nucleotide-dependent kinases.

Materials:

116. The acetoxymethylesters of Fura-2, and Fluo-4 were purchased from Molecular Probes (Eugene, Or.). Fura-2FF was purchased from Tefabs (Austin, TX). Cell permeable cyclic nucleotides and forskolin were purchased from Biomol, (Plymouth Meeting, PA). All other chemicals were purchased from Sigma Chemical Company (St. Louis, MO). The

DT-40 cells lacking $InsP_3R$ (DT-40 3ko) were kindly provided by Dr Kurosaki, (Kansai Medical University, Japan) and were maintained as previously described [42-44].

Production of Mutations:

117. The $S2^+$ $InsP_3R$-1 in the expression plasmid pIRES-GFP (Clontech; Palo Alto, CA) was digested with the restriction endonuclease Sal I. The overhang created by digestion was blunted using T4 polymerase. An EcoR I linker was then ligated onto the blunted ends of the construct. The entire receptor DNA was excised from the plasmid using EcoR I and ligated into the plasmid MXT-1. The region containing the $S2^-$ splice variant and potential PKA phosphorylation sites was excised from its backbone in pCDNA 3.1+ (Invitrogen; Carlsbad, CA) by Rsr II and Kas I and ligated into the $InsP_3R$ construct in MXT-1. The potential PKA sites, S1589 and S1755, were mutated, individually in both splice variants and together in the $S2^-$ splice variant, to alanines using sequential PCR mutagenesis. The outer oligos used for the mutagenesis reaction flanked the restriction sites Rsr II and Kas I. Following mutation, the resulting fragments were cut with Rsr II and Kas I and inserted into the IP_3R-1 backbone at the corresponding sites. The mutations and lack of spurious misincorporations were confirmed by Big Dye fluorescent sequencing. Mutated receptor DNAs were excised from MXT-1 using EcoR I and ligated into the mammalian expression vector pGW (British Biotechnology; Oxford, UK). Orientation was confirmed using restriction enzyme digestion.

Transfection of DT-40 cells:

118. DT-40 cells lacking all three $InsP_3$ receptor subtypes DT-40 3kowere transfected using electroporation, 350 V and 950 μF. 2 x 10^7 cells were co-transfected with 25 μg of the $InsP_3R$ cDNA, 25 μg of the muscarinic type 3 (M3) receptor, and 4 μg of the red fluorescent protein plasmid pHcRed1-N1. Cells were incubated with DNA in 500 μl of Optimem media on ice for 10 minutes. The cell / DNA mixture was electroporated, incubated on ice for 30 minutes, brought up to 5 ml with Optimem and placed in a 5 % CO_2 incubator at 39 °C for 5 hours. The cells were then centrifuged and resuspended in 12 ml of complete RPMI media. Transfection efficiency was typically ~20%. Experiments were performed within 32 hours of transfection.

Digital Imaging of $[Ca^{+2}]_i$:

119. Transfected DT-40 3ko cells were washed once in a HEPES-buffered physiological saline solution (HEPES-PSS) containing (in mM) 5.5 glucose, 137 NaCl, 0.56 $MgCl_2$, 4.7 KCl, 1 Na_2HPO_4, 10 HEPES (pH 7.4), 1.2 $CaCl_2$ and 1% w/v Bovine Serum Albumin. Cells

were then resuspended in BSA HEPES-PSS with 1 μM Fura-2 (AM), placed on a 15 mm glass coverslip in a low volume perfusion chamber (Warner Instruments) and allowed to adhere for 30 minutes at room temperature. Cells were perfused continually for 10 minutes with HEPES-PSS before experimentation to allow Fura-2 de-esterification. A field of cells for each experiment was chosen that contained a wide range of transfection efficiency based upon the intensity of red fluorescence emitted when excited at 560 nm. $[Ca^{2+}]_i$ imaging was performed essentially as previously described [28, 29, 41] using an inverted epifluorescence Nikon microscope with a 40X oil immersion objective lens (numerical aperture, 1.3). Cells were excited alternately with light at 340 and 380 nm (± 10 nm bandpass filters, Chroma) using a monochrometer (TILL Photonics). Fluorescence images were captured and digitized with a digital camera driven by TILL Photonics software. Images were captured every 2 seconds with an exposure of 35 ms and no binning. 340 / 380 ratio images were calculated online and stored immediately to hard disk. Only data from cells exhibiting an increase in ratio units of less than 0.2 upon stimulation were used for further analysis.

Flash Photolysis:

120. Transfected cells were simultaneously loaded by incubation with the visible wavelength indicator Fluo-4 and a cell permeable form of caged-inositol trisphosphate (ciIP$_3$/PM) for 30 min. Ci-IP$_3$/PM is a homologue of cm-IP$_3$/PM [45] The 2- and 3-hydroxyls of the inositol ring were protected by an isopropylidene group in ci-IP3/PM, and were protected by a methoxymethylene group in cm-IP$_3$/PM. Like cm-IP3/PM, ci-IP3/PM diffuses across cell membranes and induces internal calcium release upon photo-uncaging. A further period of approximately 30 min was allowed for de-esterification of both dye and cage. Cells were illuminated at 488 ± 10 nm and fluorescence collected through a 525 ± 25 nm band pass filter and captured using the Till Photonics imaging suite. These traces are displayed as % $\Delta F/F_0$, where F is the recorded fluorescence and F_0 is the mean of the initial 10 sequential frames. Photolytic release was performed as previously described [28, 29, 41] using a pulsed Xenon arc lamp (Till Photonics). A high intensity (0.5-5 msec duration; 80 J) discharge of UV light (360 ± 7.5 nm) was reflected onto the plane of focus using a DM400 dichroic mirror and Nikon X 40 oil immersion objective, 1.3 NA.

Statistical Analysis:

121. The effects of treatment were determined by normalizing the peak change in fluorescence ratio by stimulation following forskolin or 8-Br cGMP exposure to that of stimulation in control HEPES-PSS. Thus, pooled data represents a normalized fold increase

over control for the treated trial. Two tailed heteroscedastic t-tests with P values < 0.05 were considered to have statistical significance.

PKA phosphorylation of S1755 in S2$^+$ InsP$_3$R-1 resulted in enhanced Ca^{2+} release:

122. Experiments were performed in DT-40 3ko cells transfected with S2$^+$ InsP$_3$R-1. Since there are no reports of Gαq coupled receptors expressed in DT-40 cells, initial experiments were performed eliciting $[Ca^{2+}]_i$ changes by stimulating the endogenous B cell receptor with α-IgM antibody. This resulted in somewhat irregular Ca^{2+} oscillations, which were not reversible when the antibody was removed making paired analysis of any effects of raising cyclic nucleotides difficult to interpret. Thus, in all further experiments, DT-40 3ko cells were co-transfected with the M3 receptor, and HcRed to facilitate identification of transfected cells (inset fig. 1). Stimulation of M3 receptors with the muscarinic agonist carbachol (CCh), provided a convenient means of stimulating $[Ca^{2+}]_i$ changes, presumably through Gαq-induced activation of phospholipase C and production of InsP$_3$. Stimulation with a low concentration of CCh (25-50 nM) resulted in an increase in $[Ca^{2+}]_i$, which returned to baseline when the agonist was removed. Following 10 min incubation with 20 μM forskolin to maximally raise cAMP, the initial peak in $[Ca^{2+}]_i$ elicited by identical CCh treatment was markedly potentiated (fig 1A and pooled data in fig 1D). After washout of forskolin a subsequent stimulation resulted in a $[Ca^{2+}]_i$ change comparable to the initial exposure. The potentiation was most marked when threshold elevations in $[Ca^{2+}]_i$ were evoked by the initial exposure to CCh and therefore only cells in which the initial CCh treatment evoked a Δ 340/380 ratio of < 0.2 ratio units were included for analysis. These data showed that phosphorylation of the S2$^+$ InsP$_3$R resulted in enhanced Ca^{2+} release by increasing the sensitivity of the receptor to InsP$_3$. $[Ca^{2+}]_i$ changes were never evoked by CCh treatment in cells transfected with only M3 cDNA in the absence of InsP$_3$R or likewise InsP$_3$R with no M3 cDNA. Similarly, cells exhibiting no HcRed fluorescence seldom responded to CCh treatment (black trace, fig 1A).

123. To ascertain whether one or both of the serine residues S1589 or S1755 is important for phosphoregulation of the S2$^+$ variant of the InsP$_3$R-1 following PKA activation, individual point mutations were constructed where these serine residues were mutated to alanine (S1589A and S1755A). A similar potentiation of the initial peak of the CCh-induced $[Ca^{2+}]_i$ elevation was observed following forskolin treatment in cells expressing S1589A S2$^+$ InsP$_3$R (fig 1B and 1D), however mutation of S1755A resulted in the complete

abrogation of any potentiation upon forskolin treatment (fig 1C and 1D). These data clearly support the assertion that phosphorylation of S1755 is the important event underlying enhanced Ca^{2+} release through the neuronal $InsP_3R$-1 following PKA activation. It follows therefore, that phosphorylation of S1589 after 20 μM forskolin treatment (which could reasonably be expected to result in the maximal generation of cAMP) was either not occurring to a significant extent, or perhaps more likely, was functionally not important in modulating Ca^{2+} release.

124. Since the only difference between the experiment in fig 1A and 1C is a conservative point mutation in the $InsP_3R$-1, it was assumed that the effects observed on the peak Ca^{2+} signal following forskolin treatment were predominately the results of alteration of Ca^{2+} release. To rule out the possibility that phosphorylation by PKA of other signaling molecules caused the effect, experiments were performed utilizing $ciIP_3$/PM, a cell permeable form of caged $InsP_3$ [45] to more directly induce Ca^{2+} release in cells transfected with wild-type $S2^+$ $InsP_3R$-1. Using a brief flash of UV light (~ 0.5 ms, indicated by the arrow in fig 2) small elevations in $[Ca^{2+}]_i$ could be evoked. Subsequent exposure to UV light never produced an increase larger than that initially evoked, however longer flashes of UV light (5 msec) could evoke larger peak increases (fig 2A; max uncage, indicated by the large arrow-head). No effect of UV light was observed in cells either not loaded with cage, or alternatively not expressing $InsP_3R$. In contrast, when cells were incubated with 10 μM forskolin for 5 min prior to a second identical exposure to UV light a marked increase in the initial Ca^{2+} peak was evoked (fig 2B and pooled data fig 2C). This potentiation of $InsP_3$-induced release was of similar magnitude to that seen for CCh-treated cells exposed to forskolin and supports the notion that the predominant effect of forskolin treatment is to regulate Ca^{2+} release through phosphorylation of $InsP_3R$.

***PKA-induced phosphorylation of S1589 and S1755 were functionally important in the $S2^-$ $InsP_3R$-1*:**

125. The $S2^-$ variant of the $InsP_3R$-1 is predominantly expressed in peripheral tissues and in fetal brain during neuronal development [6, 7]. The $S2^-$ $InsP_3R$-1 has been reported to be phosphorylated by PKA in a number of tissues, including platelets, vas deferens, smooth muscle and hepatocytes [7, 30, 46]. In contrast to the neuronal form of the $InsP_3R$-1, studies performed with $S2^-$ $InsP_3R$-1 purified from vas deferens and smooth muscle have demonstrated that the receptor is almost exclusively phosphorylated on S1589 [7]. Reports have also suggested a different functional outcome as a result of PKA activation, since the

majority of studies, for example in megakaryocytes have suggested that phosphorylation results in inhibition of Ca^{2+} release [22]. An important caveat relevant to the interpretation of this functional data, is that in contrast to $InsP_3R$-1 in cerebellum (>99% $S2^+$ $InsP_3R$-1), in peripheral tissues multiple $InsP_3R$ types are invariably expressed to varying degrees [47]. Thus, unequivocally attributing an effect to an individual homotetrameric receptor was problematic prior to the invention.

126. Similar experimental paradigms were employed to assess the effect of PKA-induced phosphorylation on a homogeneous population of $S2^-$ $InsP_3R$-1. In DT-40 3ko cells expressing wild-type $S2^-$ $InsP_3R$-1, incubation with 20 μM forskolin for 10 min resulted in a marked potentiation of the initial CCh-induced Ca^{2+} peak (fig 3A, pooled data fig 3E) in a similar fashion to that demonstrated for the $S2^+$ $InsP_3R$-1. In contrast to the $S2^+$ variant of the $InsP_3R$-1, neither single mutation in amino acids corresponding to S1589 or S1755 in $S2^+$ $InsP_3R$-1 resulted in loss of this enhanced Ca^{2+} signal (fig 3C/3D and 3E). These data indicated that both serine residues can be phosphorylated in this form of the receptor and furthermore was consistent with the observation that the peripheral $InsP_3R$-1 is more readily phosphorylated by PKA than the neuronal form [7]. However, no potentiation was observed in cells transfected with a double mutant where both serines were mutated to alanine (S1589A/S1755A $S2^-$ $InsP_3R$-1), confirming that no additional functionally important phosphorylation sites are present in the $S2^-$ $InsP_3R$-1 (fig 3D and 3E).

127. The degree of potentiation appeared similar when comparing wild-type to either S1589A or S1755A $S2^-$ $InsP_3R$-1; expression of each construct revealed a ~3 fold increase in CCh-induced Ca^{2+} release in the presence of forskolin. These data indicated, that if the assumption is made that phosphorylation of each particular site occurred independently, that phosphorylation of individual sites appeared not to result in an additive effect on Ca^{2+} release. A potential exists, however, that the dye used in these experiments (Fura-2; kd ~150 nM) is saturated with Ca^{2+} upon CCh exposure in the presence of forskolin, thereby masking any additive effect of phosphorylating both sites. For this reason, similar experiments were performed using the lower affinity Ca^{2+} indicator Fura-2-FF (kd ~ 10 μM). While the degree of potentiation was somewhat greater in cells expressing wild-type $S2^-$ $InsP_3R$-1 (~4.5 fold) there was no significant difference in the extent of enhancement when comparing wild-type to S1589A and S1755A expressing cells (Fig 3E; filled bars). These data indicate that while it is possible that Fura-2 measurements may indeed underestimate the degree of PKA-induced enhancement of Ca^{2+} release resulting from PKA

phosphorylation, our data suggests that phosphorylation of individual sites appears not to be functionally additive.

128. To assess if the phosphorylation of a particular site was favored in S2$^-$ $InsP_3R$-1, the minimal concentration of forskolin sufficient to enhance CCh-induced Ca^{2+} release in wild-type vs. S1589A and S1755A mutants was compared. In cells transfected with wild-type S2$^-$ $InsP_3R$-1, 100 nM, 500 nM or 1 μM forskolin failed to enhance the subsequent CCh-induced Ca^{2+} release (3 experiments, >5 cells for each condition). Incubation with 5 μM forskolin resulted in a 1.26 ± 0.21 fold potentiation of Ca^{2+} release (n=6). At this threshold concentration of forskolin a similar degree of potentiation was observed in both S1589A (1.36 ± 25 fold; n=8) and S1755A (1.37 ± 0.26 fold; n=7) S2$^-$ $InsP_3R$-1. Thus, functionally, it appears that a particular site is not obviously subject to preferential phosphoregulation by PKA.

129. These data demonstrated that, in contrast to the S2$^+$ variant, both S1589 and S1755 are functionally important phosphorylation substrates in the S2$^-$ $InsP_3R$. This indicates that excision of the 40 amino acids in the S2$^-$ form of the $InsP_3R$-1 either alters the structure of the receptor allowing access to the kinase or perhaps allows the interaction with an accessory protein necessary to confer this effect. The only known structural difference between the splice variants is the insertion of an adenine nucleotide binding site in the S2$^-$ $InsP_3R$-1.

Phosphorylation of S2$^+$ $InsP_3R$-1 by PKG:

130. Similar experiments were performed to assess the effects on Ca^{2+} release of phosphorylating $InsP_3R$-1 with PKG. Cells transfected with S2$^+$ $InsP_3R$-1 together with M3 receptor and HcRed were stimulated with low, threshold concentrations of CCh (25-50 nM) followed by a 10 min treatment with 10 μM 8-Br cGMP, a specific activator of PKG [48]. Subsequent re-stimulation with an identical concentration of CCh revealed a marked potentiation of the $[Ca^{2+}]_i$ change. In a similar fashion to PKA activation, this was manifested as an increase in the CCh-induced initial peak (fig 4A and pooled data fig 4E). Moreover, these data are again consistent with phosphorylation increasing the sensitivity of the $InsP_3R$ to $InsP_3$, since sub-threshold increases in $[Ca^{2+}]_i$ were readily potentiated to substantial increases in $[Ca^{2+}]_i$ (fig 4A 4B and 4E).

131. Next, the effect of phosphorylation of S1589 and S1755 in S2$^+$ $InsP_3R$-1 mutants was assessed. In cells transfected with S1589A a similar potentiation by 8-Br cGMP was observed (fig 4B and 4E) while no enhanced $[Ca^{2+}]_i$ signal was observed in cells transfected

with S1755A (fig 4C and 4E), strongly indicating that phosphorylation of S1755 by PKG is the important event underlying this potentiation of Ca^{2+} signaling. Although PKG and PKA consensus motifs are similar (RRXS) these data are consistent with reports that S1755 is phosphorylated by PKG and furthermore that phosphorylation by PKG is enhanced by the presence of an aromatic amino acid, 4 amino acids downstream from the phosphorylatable serine as is the case for S1755 in $InsP_3R$-1 [49]. Indeed the substantial degree of potentiation may reflect the favorable nature of this site for phosphorylation by PKG. Although phosphorylation of S1755 appears to be responsible for the potentiated signal, our data thus far does not exclude the possibility that the response of wild-type $S2^+$ $InsP_3R$-1 is a result of a net phosphorylation of both serines by PKG, with phosphorylation of S1589 actually resulting in inhibited release. Thus, the effect of PKG activation on larger $[Ca^{2+}]_i$ responses to CCh stimulation was tested in cells transfected with S1589A $InsP_3R$-1. Using this paradigm no effect of 10 μM 8-Br cGMP was observed (fig 4D), confirming that either S1589 is not phosphorylated or has no functional consequence in $S2^+$ $InsP_3R$-1.

132. Although the most likely consequence of 8-Br cGMP treatment was to activate PKG, it was possible that this compound led to cAMP accumulation and activation of PKA indirectly by inhibiting cAMP phosphodiesterase [50]. Additionally, a somewhat less likely scenario was that 8-Br cGMP bound to and activated PKA directly. Experiments were therefore performed to confirm that the potentiation of Ca^{2+} signaling observed with 8-Br cGMP treatment was not the result of PKA activation. Cells transfected with $S2^+$ $InsP_3R$-1 were preincubated for 30 minutes with the cell-permeable PKA inhibitor, myristolyated PKI. This treatment completely abolished any potentiation of the CCh-induced $[Ca^{2+}]_i$ elevation after forskolin treatment (fig 5A and pooled data fig 5C). In contrast, similar treatment with PKI did not alter the potentiation induced by 8-Br cGMP treatment (fig 5B/C); this treatment still resulted in a ~20 fold potentiation of the CCh-stimulated $[Ca^{2+}]_i$ signal (compare fig 4A and fig 5B). These data clearly indicate that treatment with forskolin and 8-Br cGMP resulted in the selective activation of PKA or PKG respectively.

Phosphorylation of $S2^-$ $InsP_3R$-1 by PKG:

133. PKA or PKG phosphorylation of the $S2^-$ $InsP_3R$-1 in megakaryocytes and smooth muscle cells has been suggested to inhibit Ca^{2+} release [21, 36, 37]. This observation is difficult to reconcile with the data presented herein for phosphorylation of $S2^-$ $InsP_3R$-1 by PKA, since phosphorylation of either S1589 or S1755 resulted in potentiated release. Nevertheless, similar experiments were performed to elucidate the effect of PKG

phosphorylation of S2$^-$ $InsP_3R$-1. Interestingly, no effect of 10 μM 8-Br cGMP treatment was observed in cells transfected with either wild-type (fig 6A and pooled data fig 6D), S1589A S2$^-$ $InsP_3R$-1 (fig 6B and 6D) or S1755A S2$^-$ $InsP_3R$-1 (fig 6C and 6D). However, in the same batches of cells transfected with wild-type S2$^-$ $InsP_3R$-1, treatment with forskolin resulted in the expected ~4 fold increase in the initial peak (n=5 cells). These data also reinforced the contention that 8-Br cGMP specifically activates PKG without altering PKA activity; the logic being that if, this was not the case, activation of PKA by 8-Br cGMP in S2$^-$ $InsP_3R$-1 expressing cells would be expected to result in data similar to PKA activation shown in Fig 3.

134. The data demonstrated that PKA phosphorylation of either S1589 or S1755 resulted in enhanced Ca^{2+} release in the S2$^-$ variant of the receptor (fig 3 A/B/C). Thus, PKG is simply not capable of *directly* phosphorylating this receptor. These data, although somewhat surprising, do not rule out the possibility that phosphorylation of an accessory protein termed IRAG [51, 52] may have an effect.

135. In conclusion, using mutational analysis in a *null* $InsP_3R$ background this study has elucidated the serine residues in $InsP_3R$-1 functionally important for modulating Ca^{2+} release by cyclic nucleotide dependent protein kinases. An important finding of this study was that, although phosphorylation of either S1589 or S1755 can result in markedly enhanced Ca^{2+} release, the particular splice variant of $InsP_3R$-1 expressed dictated which sites were susceptible to phosphorylation. Potentiation of Ca^{2+} release through $InsP_3R$-1 phosphorylation thus provided a powerful means of enhancing and amplifying Ca^{2+} signaling events when multiple signaling pathways are activated. Additionally, the evidence indicated that PKG appears not to directly regulate S2$^-$ $InsP_3R$-1. Therefore, this splice variation defined which kinase is capable of phosphorylating the receptor at these sites and thus the specificity of functional response.

Example 2: Acute Regulation of Secretion: Cross-Talk Between Signaling Molecules and Their Effectors

Effects on $InsP_3$-induced Ca^{2+} release

136. Phosphorylation of inositol 1,4,5 trisphosphate receptors ($InsP_3R$) is a major point of synergism between the Ca^{2+} and cAMP signaling systems [29]. Phosphorylation of $InsP_3R$ in parotid acinar cells results in markedly enhanced Ca^{2+} release, an effect attributed to type-II $InsP_3R$ [29] . The functionally important phosphorylation sites have recently been defined in the type-I receptor [57]. The experiments examine the potential for

"phosphomimetic" mutants of $InsP_3R$-1 to enhance Ca^{2+} signaling and the mechanism responsible for this augmentation of Ca^{2+} release in both the $InsP_3R$-I and $InsP_3R$-II. These constructs can be utilized in models of impaired fluid secretion to assess their ability to augment fluid secretion.

Fluid secretion in salivary acinar cells

137. Appropriate control of salivary secretion is required for effective speech, mastication and general oral health [62-64]. Disruption of normal secretion is thus a significant health problem for affected individuals. The inability to produce an adequate salivary fluid secretion results in a variety of conditions that together comprise a major health problem for a significant proportion of the population [62, 63].

138. Fluid secretion in the salivary glands relies on the secondary active transepithelial transport of Cl^- [61, 65-68]. Briefly, Cl^- ions enter the cell across the basolateral membrane, in part via Cl^-/HCO_3^- exchange but primarily by an electrically neutral Na^+-K^+-$2Cl^-$ cotransport process [69-72]. The accumulated K^+ ions recycle to the serosal side via basolateral K^+ channels, whilst the accumulated Cl^- exit to the mucosal side via apical Cl^- channels. The resultant transepithelial movement of Cl^- generates an electrical potential gradient (lumen negative) sufficient to drive Na^+ into the lumen via a paracellular pathway. The net result is the secretion of Na^+ and Cl^-, with water following osmotically [61, 65, 68]. The principal means of regulation of this fluid secretion involves stimulation via parasympathetic nerves supplying the glands [73]. It is generally acknowledged that the main component of this system involves neurally released acetylcholine (ACh) acting at muscarinic receptors on the acinar cells [74-76]. Activation of these receptors produces a rise in $[Ca^{2+}]_i$ as a result of an increased turnover of membrane phosphoinositides and the generation of inositol 1,4,5-trisphosphate ($InsP_3$) [77]. The elevated $[Ca^{2+}]_i$ in turn acts at membrane ion channels, specifically increasing basolateral K^+ conductance and an apical Cl^- conductance [61, 65, 67, 68]. It is the increases in these conductance pathways that lead to the initiation of the secretion of ions and accompanying fluid. The rise in $[Ca^{2+}]_i$ also apparently has important additional effects including the stimulation of the activity of the basolateral Na^+-K^+-$2Cl^-$ cotransport increasing the entry of Cl^- ions into the cell [78].

Ca^{2+} signaling in parotid acinar cells

139. Many studies have investigated the characteristics of $[Ca^{2+}]_i$ signals in parotid acinar cells [79]. In common with other electrically non-excitable cells, cytosolic Ca^{2+} signals comprise both the release of Ca^{2+} from intracellular stores and the activation of pathways mediating the entry of Ca^{2+} from the extracellular space. It should be noted that while the

release of intracellular Ca^{2+} is capable of initiating fluid secretion in the salivary glands, the ability to produce a sustained secretion is known to be entirely dependent on the influx of Ca^{2+} from the extracellular medium [58-60]. Consequently, a thorough understanding of the processes leading to activation and modulation of both Ca^{2+} release and Ca^{2+} influx is fundamentally important for understanding fluid secretion.

140. The pathways involved in Ca^{2+} release are relatively well defined; the binding of secretagogues such as ACh, substance P, noradrenaline and ATP (acting at P2Y receptors) to plasma membrane receptors, couples to the heterotrimeric G protein Gαq/11, resulting in activation of PLCβ and the subsequent formation of $InsP_3$. All three isoforms of $InsP_3R$ are expressed to varying degrees in rodent parotid tissue, with ~80% comprising the type-II ($InsP_3R$-II) or type-III isoform ($InsP_3R$-III) and with $InsP_3R$-II constituting the absolute majority [80, 81]. Binding of $InsP_3$ to these receptors located in the endoplasmic reticulum results in explosive Ca^{2+} release into the cell cytoplasm. The vast majority of $InsP_3R$ are expressed in the extreme apical pole of the cells and this localization reasonably explains why Ca^{2+} release is initiated in this region [82, 53]. Physiologically, the initial increase in $[Ca^{2+}]_i$ is ideally situated to activate Ca^{2+}-dependent Cl^- channels which are localized exclusively to the luminal membrane [54]. Subsequently, the $[Ca^{2+}]_i$ signal rapidly becomes "global", facilitating the activation of basolateral Ca^{2+}-activated K^+ channels [80]. The process responsible for the extremely rapid globalization of the Ca^{2+} signal appears to be distinct from other exocrine cells, such as pancreatic acinar cells [80], in that the increase is much too rapid to be mediated by a classical Ca^{2+} wave propagated by sequentially Ca^{2+}-induced Ca^{2+} release from neighboring release sites . Instead, experimental evidence and mathematical modeling indicate that this phenomenon is best explained by largely autonomous, local Ca^{2+} release occurring throughout the cytoplasm mediated by both ryanodine receptors (RyR) and $InsP_3R$ [80, 55].

141. Importantly this secretagogue-induced Ca^{2+} release is modulated in both mouse and human parotid acinar cells under conditions where cAMP is elevated. cAMP results in a substantial increase in the $[Ca^{2+}]_i$ signal upon muscarinic stimulation relative to stimulation in the absence of cAMP. In particular the initial increase in $[Ca^{2+}]_i$ was enhanced, sub-threshold stimulation was transformed to a measurable $[Ca^{2+}]_i$ increase and an oscillatory increase was converted to a sustained $[Ca^{2+}]_i$ increase, all consistent with a left shift in sensitivity to stimulation by Ca^{2+} mobilizing agonists. Although, there are obviously many potential molecular targets of cAMP, these studies indicated that modulation by cAMP of

PLC activity, pumping activity through PMCA or SERCA, and release through RyR did not appear to be responsible for the enhanced $[Ca^{2+}]_i$ signal [29, 57]. Instead the major effect appeared to be enhanced Ca^{2+} release through PKA phosphorylation of $InsP_3R$. Moreover, this effect was attributed in particular to the $InsP_3R$-II since this isoform has the greatest sensitivity to $InsP_3$, is the most abundant in mouse parotid, and was shown to be specifically phosphorylated [29]. Since $InsP_3R$ are central to mobilizing $[Ca^{2+}]_i$ in parotid acinar cells, their regulation by phosphorylation provides a point of convergence whereby any secretagogues acting through Gq-PLC are subject to modulation. Indeed, this appears to be the case since Ca^{2+} release through P2Y purinoreceptors in mouse acini is also is enhanced by cAMP treatment.

142. While the functional consequences of $InsP_3R$ phosphorylation appear to be sub-type specific, recent studies in heterologous expression systems have demonstrated that phosphorylation of $InsP_3R$-I in addition to $InsP_3R$-II also leads to markedly enhanced Ca^{2+} release. The particular sites within $InsP_3R$-I which are functionally important for potentiated release have also been defined; two canonical PKA-phosphorylation motifs which are conserved from Drosophila to human are present in the $InsP_3R$-1 sequence but are not present in either the $InsP_3R$-II or $InsP_3R$-III [12]. In the splice variant of the $InsP_3R$-1 expressed in parotid acinar cells ($S2^-$ $InsP_3R$-1 or "short form") [7] phosphorylation of both sites occurs, resulting in $InsP_3R$ with an enhanced apparent sensitivity to $InsP_3$. Because potentiation of Ca^{2+} release at the level of $InsP_3R$ can be a nexus for interactions between the cAMP and Ca^{2+} signaling systems in parotid acinar cells, this project investigates the mechanism underpinning this effect by studying $InsP_3R$ with phosphomimetic mutations. These receptors can be used therapeutically to maximize $[Ca^{2+}]_i$ signals if expressed in diseased salivary tissue.

$InsP_3$-dependent Ca^{2+} release: *cAMP effects on Ca^{2+} release*

143. In mouse parotid acinar cells raising cAMP profoundly potentiates muscarinic agonist-induced $[Ca^{2+}]_i$ signals [29, 83, 84]. A major mechanism underlying this phenomenon can be the PKA-dependent phosphorylation of $InsP_3R$ [29]. The primary evidence supporting this is that cAMP elevation results in both $InsP_3R$ phosphorylation and a marked potentiation of Ca^{2+} release in a PKA dependent manner [29]. Data, consistent with the idea that $InsP_3R$ are central to this effect, is presented in Fig. 7. First, Ca^{2+} release generated through other Gq/PLC-linked receptors, such as P2Y purinergic receptors were also enhanced by cAMP elevation (Fig. 7A). Secondly, the effect was not species specific since a similar marked potentiation of the CCh-induced elevation in $[Ca^{2+}]_i$ was observed in

human parotid acini incubated with either forskolin (Fig. 7B) or β-adrenergic agonist prior to stimulation. The effects of $InsP_3R$ phosphorylation can be subtype-specific. Enhanced Ca^{2+} release is consistent with an effect on $InsP_3R$-II as this $InsP_3R$ is most abundant in parotid tissue and PKA-dependent phosphorylation of $InsP_3R$-II has been shown to augment Ca^{2+} release in other tissues such as liver [30]. It should be noted however, that all three subtypes of $InsP_3R$ are expressed in parotid tissue with similar localization to the apical domain of the cell.

144. Experiments expressing in the DT-40 3kocells a mutant $InsP_3$ R-1 where serine residues at position 1589 and 1755 are mutated to glutamate as described above, result in markedly potentiated Ca^{2+} release (Fig. 8).

145. Phosphorylation of $InsP_3R$ can alter apparent sensitivity to $InsP_3$ by a number of mechanisms. These include altering the sensitivity to $InsP_3$ itself, by changing the sensitivity of the receptor to its co-agonist Ca^{2+} or alternatively by modulating the interaction with other regulatory factors such as proteins or adenine nucleotides. Although studying Ca^{2+} release in DT-40 3ko cells as described above provides a powerful system to assess the net cellular effect of phosphorylation, a complimentary approach can be employed to study the biophysical properties of single $InsP_3R$ channels in isolated nuclei from cells overexpressing $InsP_3R$ and mutants. This technique relies on the fact that the outer nuclear membrane is continuous with the ER and can be patch clamped in the "on nucleus" configuration [11, 85-89]. Studies have successfully recorded $InsP_3$ dependent currents from isolated Cos-7 nuclei overexpressing $InsP_3R$-1 (Fig. 9). Because of the very low expression of endogenous $InsP_3R$ in Cos-7 cells [11, 88] $InsP_3$-dependent channel activity in untransfected/mock transfected cells has not been observed. In the example shown in Fig. 9, representative sweeps are shown from a single nucleus which was patched on 6 separate occasions; initially with saturating $InsP_3$, subsequently with no $InsP_3$, and then later again with $InsP_3$ in the patch pipette.

Example 3: Modulation of Ca^{2+} Release by Inositol 1,4,5-trisphosphate Receptor Phosphorylation

146. Inositol 1,4,5-trisphosphate receptors ($InsP_3R$) are the major route of intracellular calcium release in eukaryotic cells and thus are pivotal for stimulation of Ca^{2+} dependent effectors important for the control of numerous physiological processes (Figures 10 and 11). Modulation of Ca^{2+} release through $InsP_3R$ is thus of general importance for defining the particular spatio-temporal characteristics of Ca^{2+} signals. While it is widely appreciated that

Ca^{2+} itself is an important regulator of $InsP_3R$, the receptor is also subject to modulation through numerous inputs, including protein-protein interactions, binding of adenine nucleotides and phosphorylation by multiple kinases. In this study, the effects on Ca^{2+} release of phosphorylation of $InsP_3R$ by cyclic nucleotide-dependent protein kinases was studied.

147. To investigate the particular sites of phosphoregulation in an unambiguously homogenous population of homomeric receptors, type-1 $InsP_3R$ ($InsP_3R$-I) were expressed in DT-40 cells devoid of endogenous $InsP_3R$ (Figure 1A) (43). In cells expressing the neuronal, $S2^+$ splice variant of the $InsP_3R$-1, Ca^{2+} release was markedly enhanced when either PKA or PKG was activated (Figure 1B-D and as described above) (23). The sites of phosphorylation were investigated by mutation of serine residues present in two canonical phosphorylation sites present in the protein. Potentiated Ca^{2+} release was abolished when serine 1755 was mutated to alanine (S1755A) but was unaffected by a similar mutation of serine 1589 (S1589A) (Figures 3 and 12). These data demonstrate that S1755 is the functionally important residue for phosphoregulation by PKA and PKG in the neuronal variant of the $InsP_3R$-1. Activation of PKA also resulted in potentiated Ca^{2+} release in cells expressing the non-neuronal, $S2^-$ splice variant of the $InsP_3R$-1. However, the PKA-induced potentiation was still evident in S1589A or S1755A $InsP_3R$-1 mutants. The effect was abolished in the double (S1589A/S1755A) mutant, indicating both sites are phosphorylated and contribute to the functional effect (Figure 8). Indeed, mimicking phosphorylation by changing either S1589 or S1755 to a positively charged glutamate residue (S1589E or S1755E) resulted in $InsP_3R$ with apparent enhanced sensitivity to $InsP_3$ (Figures 8 and 13). Activation of PKG had no effect on Ca^{2+} release in cells expressing the $S2^-$ variant of $InsP_3R$-1. Collectively these data indicated that phosphoregulation of $InsP_3R$-1 had dramatic effects on Ca^{2+} release and defined the molecular sites phosphorylated in the major variants expressed in neuronal and peripheral tissues.

148. Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains. The references disclosed are also individually and specifically incorporated by reference herein for the material contained in them that is discussed in the sentence in which the reference is relied upon.

149. It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the

invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

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IV. CLAIMS

What is claimed is:

1. A $InsP_3R$ mutant, comprising at least one substitution of serine for a negatively charged amino acid residue at a phosphorylation site of a wild-type $InsP_3R$, wherein the mutant has an enhanced Ca^{2+} release function as compared to the wild-type $InsP_3R$.

2. The mutant of claim 1, wherein the Ca^{2+} release function is at least 5 times greater than the Ca^{2+} release function of the wild-type $InsP_3R$.

3. The mutant of claim 1, wherein the $InsP_3R$ mutant is an $InsP_3R$-1 mutant and the wild-type $InsP_3R$ is $InsP_3R$-1.

4. The mutant of claim 3, comprising at least one substitution of serine for a negatively charged amino acid residue at a phosphorylation site, wherein the phosphorylation site is selected from residue 1589 or 1755 of a wild–type $InsP_3R$-1 sequence.

5. The mutant of claim 4, wherein the substitution of serine for the negatively charged amino acid is at residue 1589.

6. The mutant of claim 4, wherein glutamate is substituted for serine at residue 1589.

7. The mutant of claim 6, wherein the mutant comprises the amino acid sequence of SEQ ID NO:1.

8. The mutant of claim 6, wherein the mutant comprises the amino acid sequence of SEQ ID NO:1 with one or more conservative amino acid substitutions.

9. The mutant of claim 6, wherein the mutant comprises the amino acid sequence of SEQ ID NO:2.

10. The mutant of claim 6, wherein the mutant comprises the amino acid sequence of SEQ ID NO:2 with one or more conservative amino acid substitutions.

11. The mutant of claim 4, wherein aspartate is substituted for serine at residue 1589.

12. The mutant of claim 11, wherein the mutant comprises the amino acid sequence of SEQ ID NO:3.

13. The mutant of claim 11, wherein the mutant comprises the amino acid sequence of SEQ ID NO:3 with one or more conservative amino acid substitutions.

14. The mutant of claim 11, wherein the mutant comprises the amino acid sequence of SEQ ID NO:4.

15. The mutant of claim 11, wherein the mutant comprises the amino acid sequence of SEQ ID NO:4 with one or more conservative amino acid substitutions.

16. The mutant of claim 4, wherein the substitution of serine for the negatively charged amino acid is at residue 1755.

17. The mutant of claim 16, wherein glutamate is substituted for serine at residue 1755.

18. The mutant of claim 17, wherein the mutant comprises the amino acid sequence of SEQ ID NO:5.

19. The mutant of claim 17, wherein the mutant comprises the amino acid sequence of SEQ ID NO:5 with one or more conservative amino acid substitutions.

20. The mutant of claim 17, wherein the mutant comprises the amino acid sequence of SEQ ID NO:6.

21. The mutant of claim 17, wherein the mutant comprises the amino acid sequence of SEQ ID NO:6 with one or more conservative amino acid substitutions.

22. The mutant of claim 16, wherein aspartate is substituted for serine at residue 1755.

23. The mutant of claim 22, wherein the mutant comprises the amino acid sequence of SEQ ID NO:7.

24. The mutant of claim 22, wherein the mutant comprises the amino acid sequence of SEQ ID NO:7 with one or more conservative amino acid substitutions.

25. The mutant of claim 22, wherein the mutant comprises the amino acid sequence of SEQ ID NO:8.

26. The mutant of claim 22, wherein the mutant comprises the amino acid sequence of SEQ ID NO:8 with one or more conservative amino acid substitutions.

27. The mutant of claim 4, wherein the substitutions of serine for the negatively charged amino acid is at residues 1589 and 1755.

28. The mutant of claim 27, wherein glutamate is substituted for serine at residues 1589 and 1755.

29. The mutant of claim 28, wherein the mutant comprises the amino acid sequence of SEQ ID NO:9.

30. The mutant of claim 28, wherein the mutant comprises the amino acid sequence of SEQ ID NO:9 with one or more conservative amino acid substitutions.

31. The mutant of claim 28, wherein the mutant comprises the amino acid sequence of SEQ ID NO:10.

32. The mutant of claim 28, wherein the mutant comprises the amino acid sequence of SEQ ID NO:10 with one or more conservative amino acid substitutions.

33. The mutant of claim 27, wherein aspartate is substituted for serine at residues 1589 and 1755.

34. The mutant of claim 33, wherein the mutant comprises the amino acid sequence of SEQ ID NO:11.

35. The mutant of claim 33, wherein the mutant comprises the amino acid sequence of SEQ ID NO:11 with one or more conservative amino acid substitutions.

36. The mutant of claim 33, wherein the mutant comprises the amino acid sequence of SEQ ID NO:12.

37. The mutant of claim 33, wherein the mutant comprises the amino acid sequence of SEQ ID NO:12 with one or more conservative amino acid substitutions.

38. The mutant of claim 27, wherein aspartate is substituted for serine at residue 1589 and glutamate is substituted for serine at residue 1755.

39. The mutant of claim 37, wherein the mutant comprises the amino acid sequence of SEQ ID NO:13.

40. The mutant of claim 37, wherein the mutant comprises the amino acid sequence of SEQ ID NO:13 with one or more conservative amino acid substitutions.

41. The mutant of claim 37, wherein the mutant comprises the amino acid sequence of SEQ ID NO:14.

42. The mutant of claim 37, wherein the mutant comprises the amino acid sequence of SEQ ID NO:14 with one or more conservative amino acid substitutions.

43. The mutant of claim 25, wherein glutamate is substituted for serine at residue 1589 and aspartate is substituted for serine at residue 1755.

44. The mutant of claim 43, wherein the mutant comprises the amino acid sequence of SEQ ID NO:15.

45. The mutant of claim 43, wherein the mutant comprises the amino acid sequence of SEQ ID NO:15 with one or more conservative amino acid substitutions.

46. The mutant of claim 43, wherein the mutant comprises the amino acid sequence of SEQ ID NO:16.

47. The mutant of claim 43, wherein the mutant comprises the amino acid sequence of SEQ ID NO:16 with one or more conservative amino acid substitutions.

48. A nucleic acid that encodes the mutant of claim 1-47.

49. An expression vector comprising the nucleic acid of claim 48 operable linked to an expression control sequence.

50. A cultured cell comprising the vector of claim 48.

51. The cell of claim 50, wherein the cell is a DT-40 cell.

52. The cell of claim 51, wherein the cell further comprises a nucleic acid that encodes an acetylcholine receptor.

53. The cell of claim 52, wherein the acetylcholine receptor is an M3 receptor.

54. An $InsP_3R$ mutant, comprising at least one substitution of serine for an amino acid with an aliphatic side chain at a phosphorylation site of a wild-type $InsP_3R$, wherein the mutant is nonphosphorylatable.

55. The mutant of claim 50, wherein the nonphosphorylatable mutant is an $InsP_3R$-1 mutant.

56. The mutant of claim 50, wherein the nonphosphorylatable mutant of $InsP_3R$ is selected from the group consisting of an S1755A, or S1589A/S1755A mutation.

57. A nucleic acid that encodes the mutant of claim50.

58. An expression vector comprising the nucleic acid of claim 57 operable linked to an expression control sequence.

59. A cultured cell comprising the vector of claim 57.

60. The cell of claim 59, wherein the cell is a DT-40 cell.

61. The cell of claim 60 wherein the cell further comprises a nucleic acid that encodes an acetylcholine receptor.

62. The cell of claim 61, wherein the acetylcholine receptor is an M3 receptor.

63. A method of screening for an agent that preferentially modulates Ca^{2+} release by phosphorylated $InsP_3R$, comprising

a. contacting the cell of claim 50 with the agent to be screened, under conditions that allow Ca^{2+} release;

b. measuring Ca^{2+} release; and

c. comparing the amount of Ca^{2+} release in step b with a control cell, wherein the control cell comprises an un-phosphorylated $InsP_3R$ and wherein the control cell is contacted with the agent to be screened, an increase or decrease in Ca^{2+} release as compared to a control cell indicating an agent that preferentially modulates unphosphorylated $InsP_3R$.

64. The method of claim 63, wherein the un-phosphorylated $InsP_3R$ is a nonphosphorylatable mutant $InsP_3R$.

65. The method of claim 64, wherein the nonphosphorylatable mutant comprises a substitution of a serine at a phosphoylation site with an amino acid having an aliphatic side-chain.

66. The method of claim 65, wherein the amino acid having an aliphatic side chain is alanine.

67. The method of claim 65, wherein the phosphorylaytion site is either residue 1589 or1755 or a combination thereof of wild-type $InsP_3R$.

68. A method of expressing a mutant $InsP_3R$ in a cell *in vivo*, comprising

a. providing the expression vector of claim 48;

b. introducing the vector into a cell *in vivo*;

c. maintaining the cell under condition that permit expression of the mutant $InsP_3R$ by the cell.

69. A method of treating a subject with xerostomia, comprising introducing into the subject the expression vector of claim 48 under conditions that an amount of $InsP_3R$ mutant is expressed in an effective amount to alleviate the symptoms of xerostomia.

70. A method of treating a subject with cystic fibrosis, comprising introducing into the subject the expression vector of claim 48 under conditions that an amount of $InsP_3R$ mutant is expressed in an effective amount to alleviate the symptoms of cystic fibrosis.

71. The mutant of claim 1, wherein the $InsP_3R$ mutant is an $InsP_3R$-2 mutant and the wild-type $InsP_3R$ is $InsP_3R$-2.

72. The mutant of claim 71, comprising at least one substitution of serine for a negatively charged amino acid residue at a phosphorylation site, wherein the phosphorylation site is selected from residue 766, 1772, 1856, 2058; 2227 of a wild–type $InsP_3R$-2 sequence.

73. The mutant of claim 72, wherein one or more serines are substituted with glutamate.

74. The mutant of claim 72, wherein one or more serines are substituted with aspartate.

75. The mutant of claim 72, wherein any combination of the serines are substituted with any combination of aspartate or glutamate.

76. The mutant of claim 1, wherein the $InsP_3R$ mutant is an $InsP_3R$-3 mutant and the wild-type $InsP_3R$ is $InsP_3R$-3.

77. The mutant of claim 76, comprising at least one substitution of serine for a negatively charged amino acid residue at a phosphorylation site, wherein the phosphorylation site is selected from residue 934, 1640, 1834, 2009, 2041, 2189 of a wild–type $InsP_3R$-3 sequence.

78. The mutant of claim 77, wherein one or more serines are substituted with glutamate.

79. The mutant of claim 77, wherein one or more serines are substituted with aspartate.

80. The mutant of claim 77, wherein any combination of the serines are substituted with any combination of aspartate or glutamate.

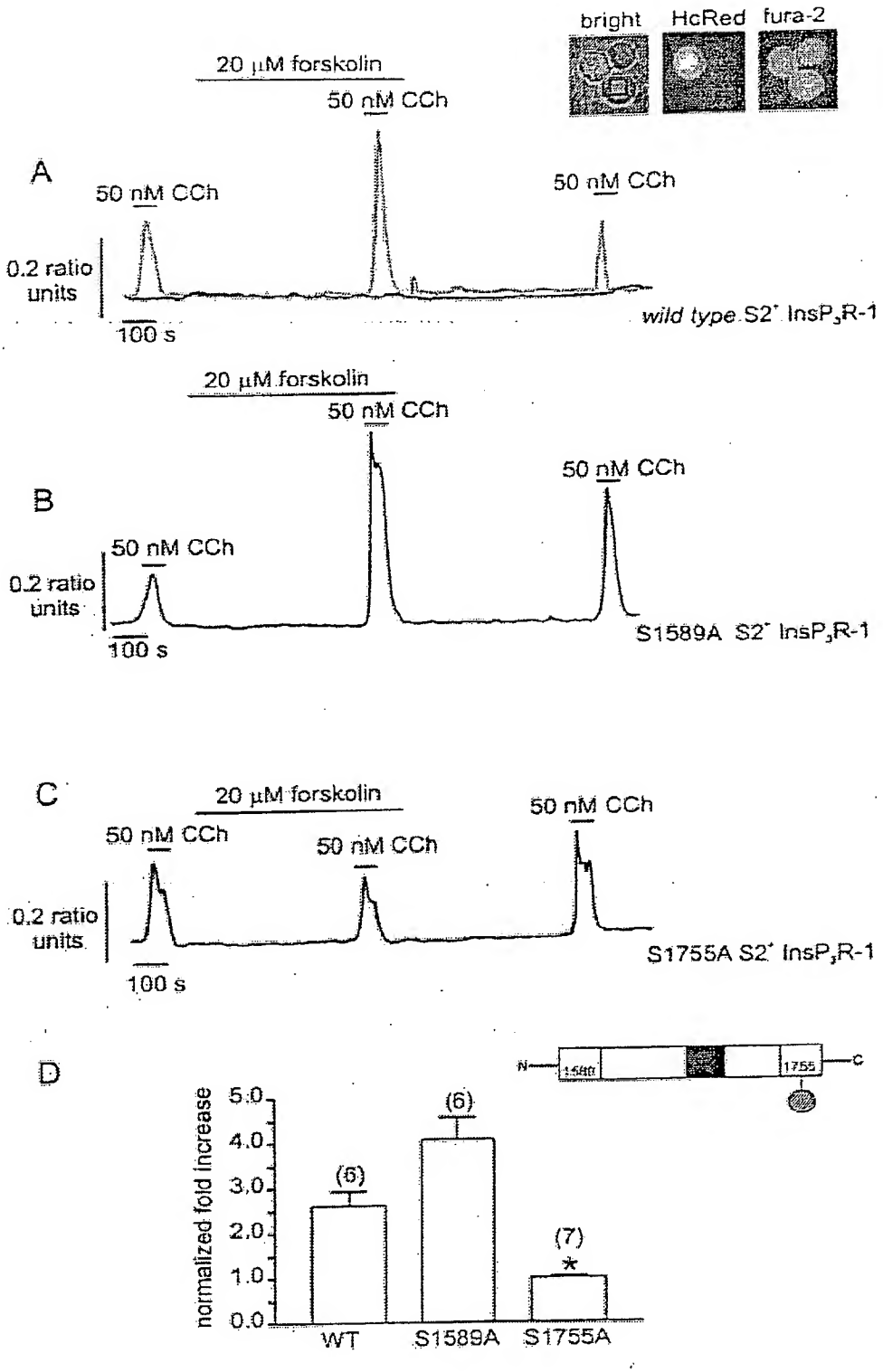

bright
HcRed
fura-2
20 μM forskolin
50 nM CCh
A
50 nM CCh
50 nM CCh
0.2 ratio units
100 s
wild type S2+ InsP3R-1
20 μM forskolin
50 nM CCh
B
50 nM CCh
50 nM CCh
0.2 ratio units
100 s
S1589A S2+ InsP3R-1
C
20 μM forskolin
50 nM CCh
50 nM CCh
50 nM CCh
0.2 ratio units
100 s
S1755A S2+ InsP3R-1
D
N
1589
1755
C
normalized fold increase
5.0
4.0
3.0
2.0
1.0
0.0
(6)
(6)
(7)
*
WT
S1589A
S1755A

FIG. 1

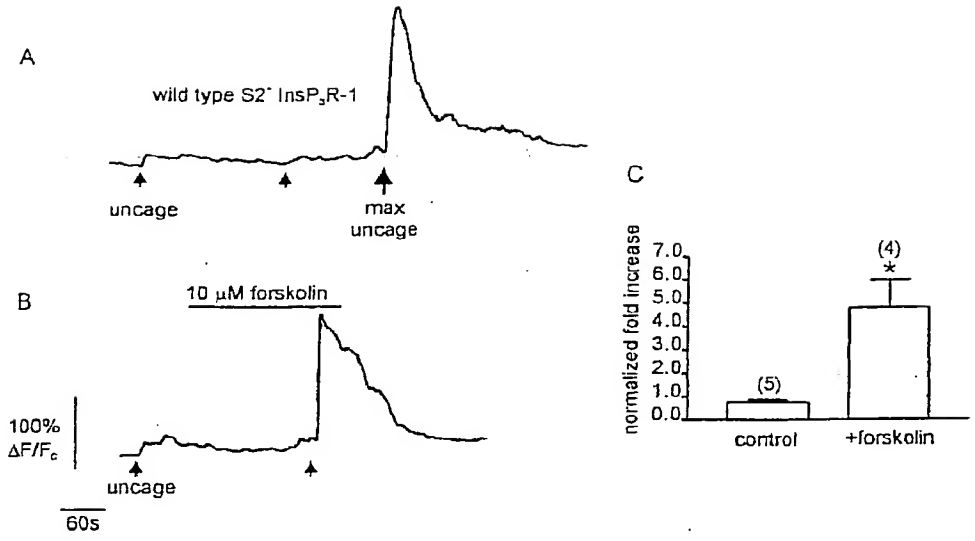

A
wild type S2⁻ InsP3R-1
uncage
max uncage
B
10 μM forskolin
100% ΔF/Fc
uncage
60s
C
normalized fold increase
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(5)
(4)
*
control
+forskolin

FIG. 2

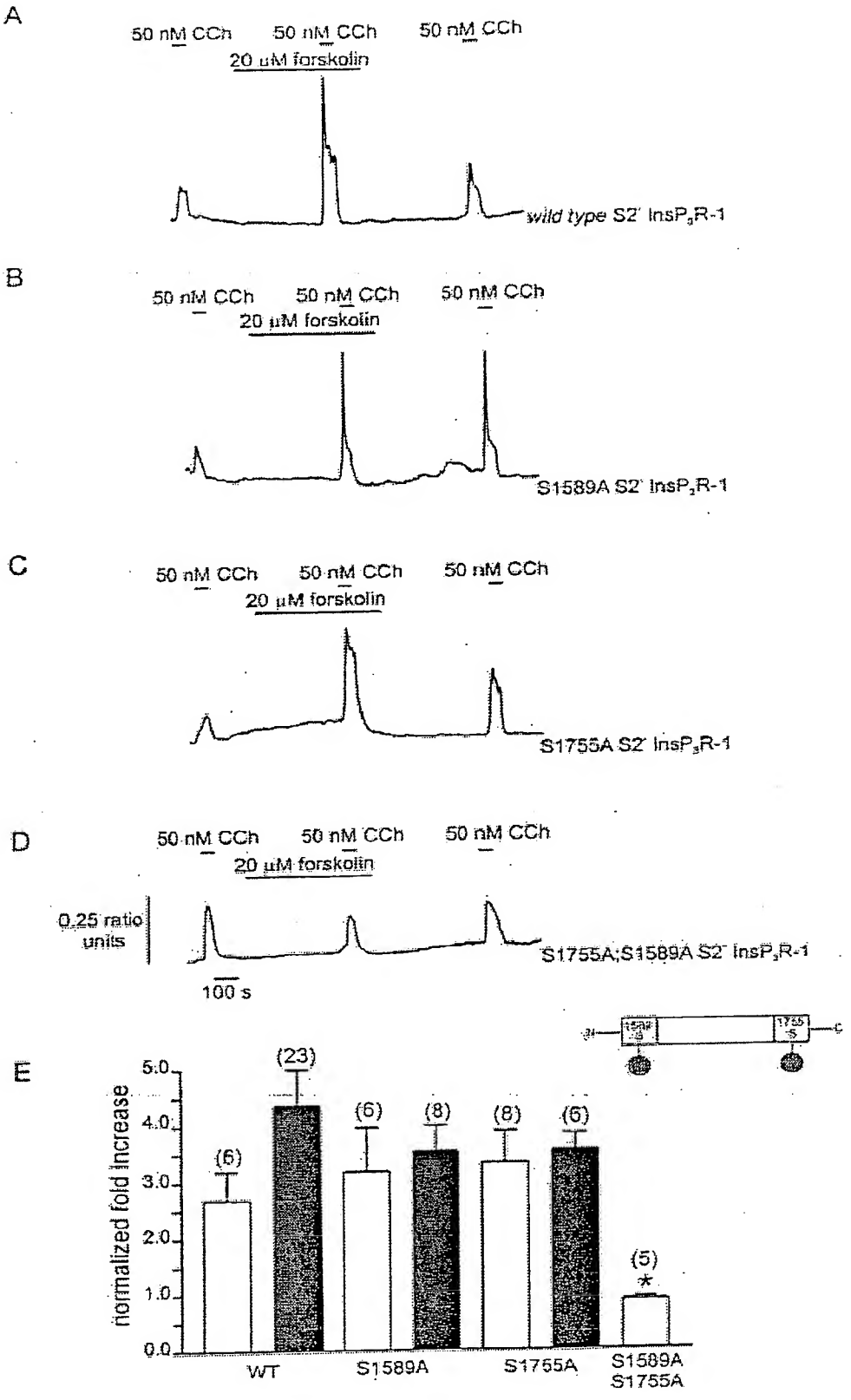

A
50 nM CCh
50 nM CCh
50 nM CCh
20 μM forskolin
wild type S2+ InsP3R-1
B
50 nM CCh
50 nM CCh
50 nM CCh
20 μM forskolin
S1589A S2+ InsP3R-1
C
50 nM CCh
50 nM CCh
50 nM CCh
20 μM forskolin
S1755A S2+ InsP3R-1
D
50 nM CCh
50 nM CCh
50 nM CCh
20 μM forskolin
0.25 ratio units
100 s
S1755A;S1589A S2+ InsP3R-1
E
normalized fold increase
5.0
4.0
3.0
2.0
1.0
0.0
(6)
(23)
(6)
(8)
(8)
(6)
(5)
*
WT
S1589A
S1755A
S1589A S1755A

FIG. 3

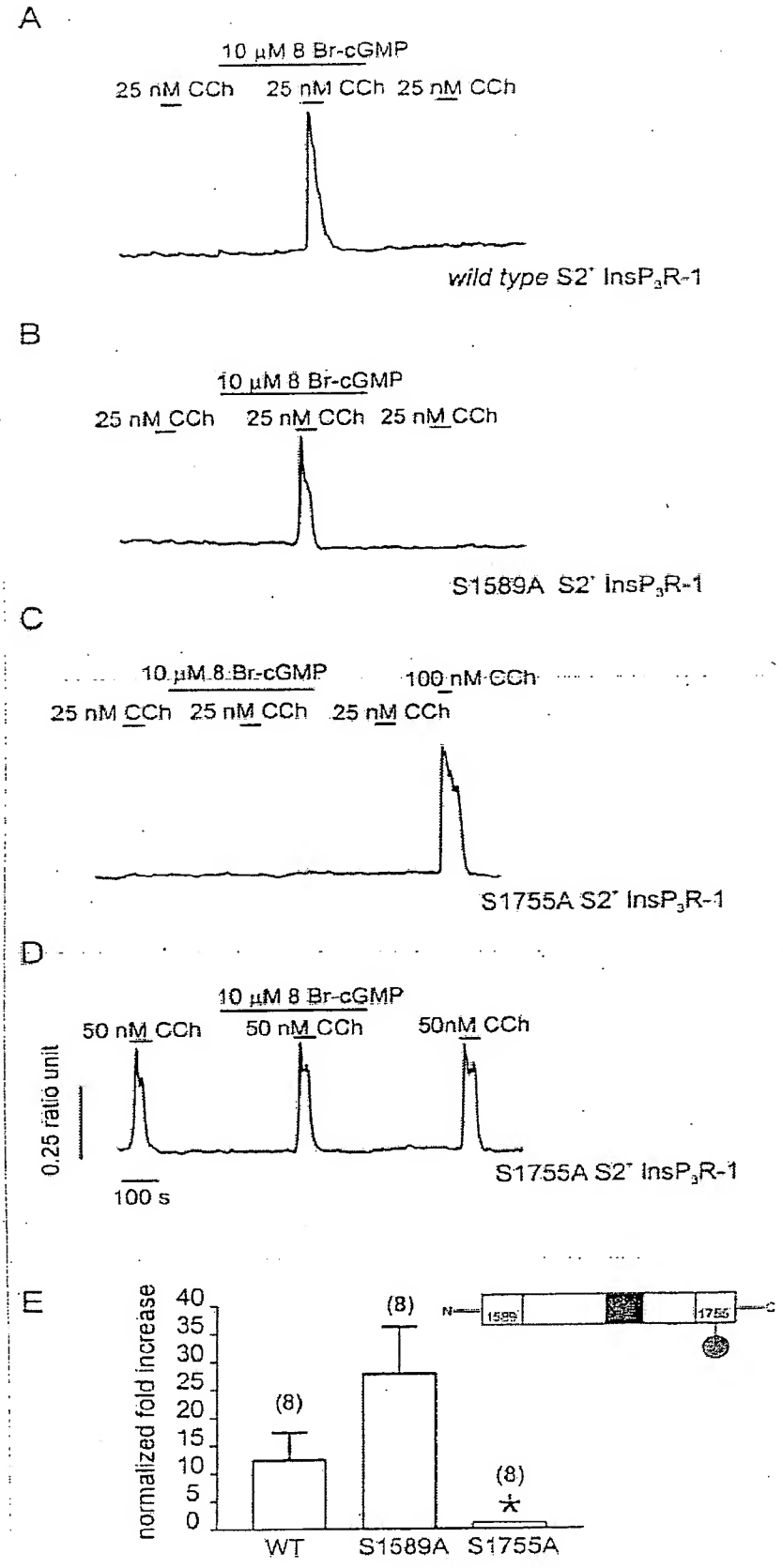
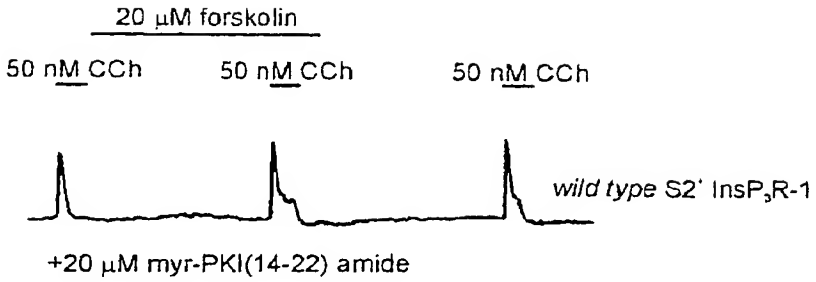
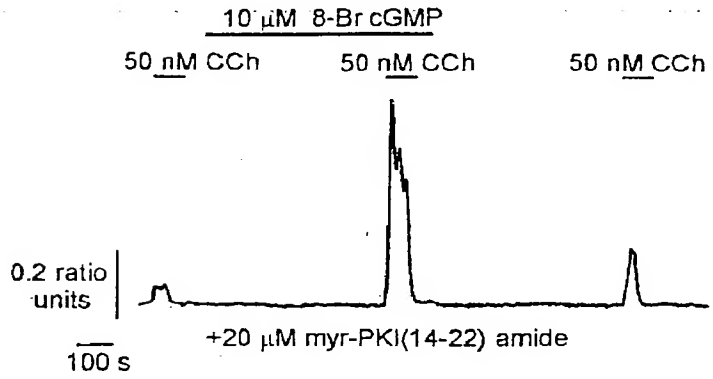

A
10 μM 8 Br-cGMP
25 nM CCh
25 nM CCh
25 nM CCh
wild type S2' InsP3R-1
B
10 μM 8 Br-cGMP
25 nM CCh
25 nM CCh
25 nM CCh
S1589A S2' InsP3R-1
C
10 μM 8 Br-cGMP
100 nM CCh
25 nM CCh
25 nM CCh
25 nM CCh
S1755A S2' InsP3R-1
D
10 μM 8 Br-cGMP
50 nM CCh
50 nM CCh
50nM CCh
0.25 ratio unit
100 s
S1755A S2' InsP3R-1
E
normalized fold increase
40
35
30
25
20
15
10
5
0
(8)
(8)
(8)
N
1589
1755
C
WT
S1589A
S1755A

FIG. 4

A


20 μM forskolin
50 nM CCh
50 nM CCh
50 nM CCh
wild type S2' InsP3R-1
+20 μM myr-PKI(14-22) amide

B


10 μM 8-Br cGMP
50 nM CCh
50 nM CCh
50 nM CCh
0.2 ratio units
100 s
+20 μM myr-PKI(14-22) amide

C

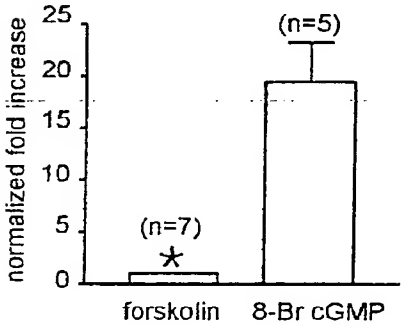

normalized fold increase
25
20
15
10
5
0
(n=5)
(n=7)
*
forskolin
8-Br cGMP

FIG. 5

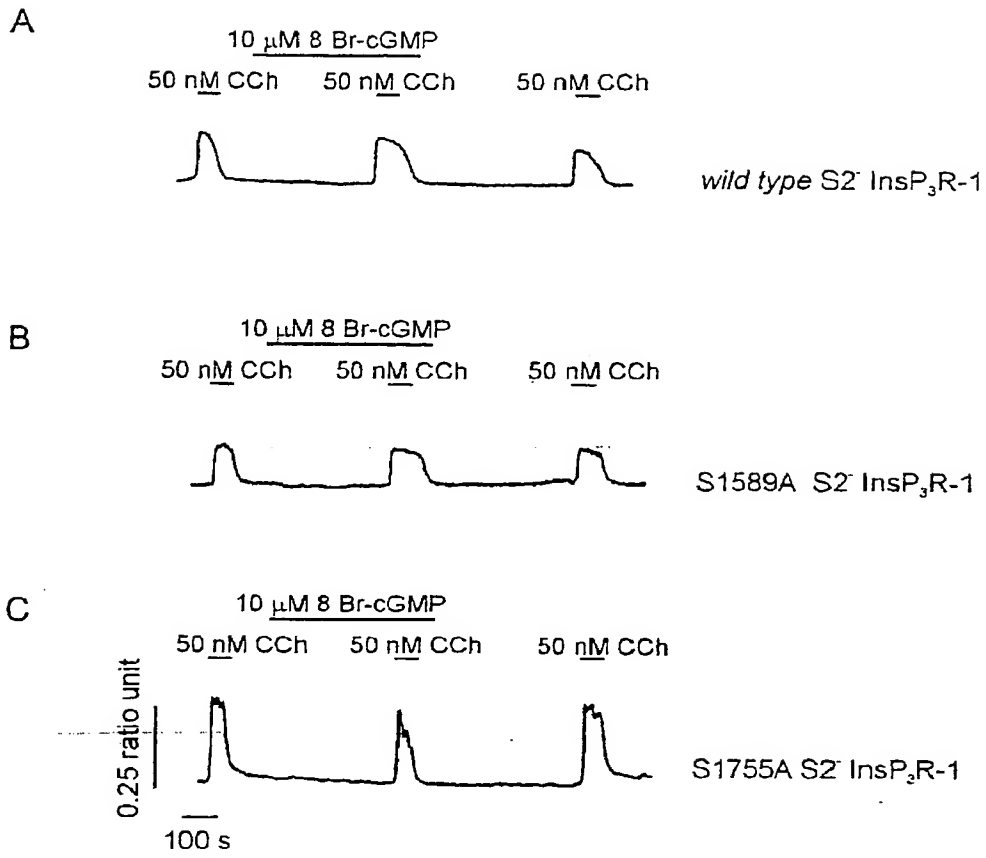

A
10 μM 8 Br-cGMP
50 nM CCh
50 nM CCh
50 nM CCh
wild type S2- InsP3R-1
B
10 μM 8 Br-cGMP
50 nM CCh
50 nM CCh
50 nM CCh
S1589A S2- InsP3R-1
C
10 μM 8 Br-cGMP
50 nM CCh
50 nM CCh
50 nM CCh
0.25 ratio unit
100 s
S1755A S2- InsP3R-1
D
normalized fold increase
5.0
4.0
3.0
2.0
1.0
0.0
(8)
(5)
(8)
WT
S1589A
S1755A
N
1589 S
1755 S
C

FIG. 6

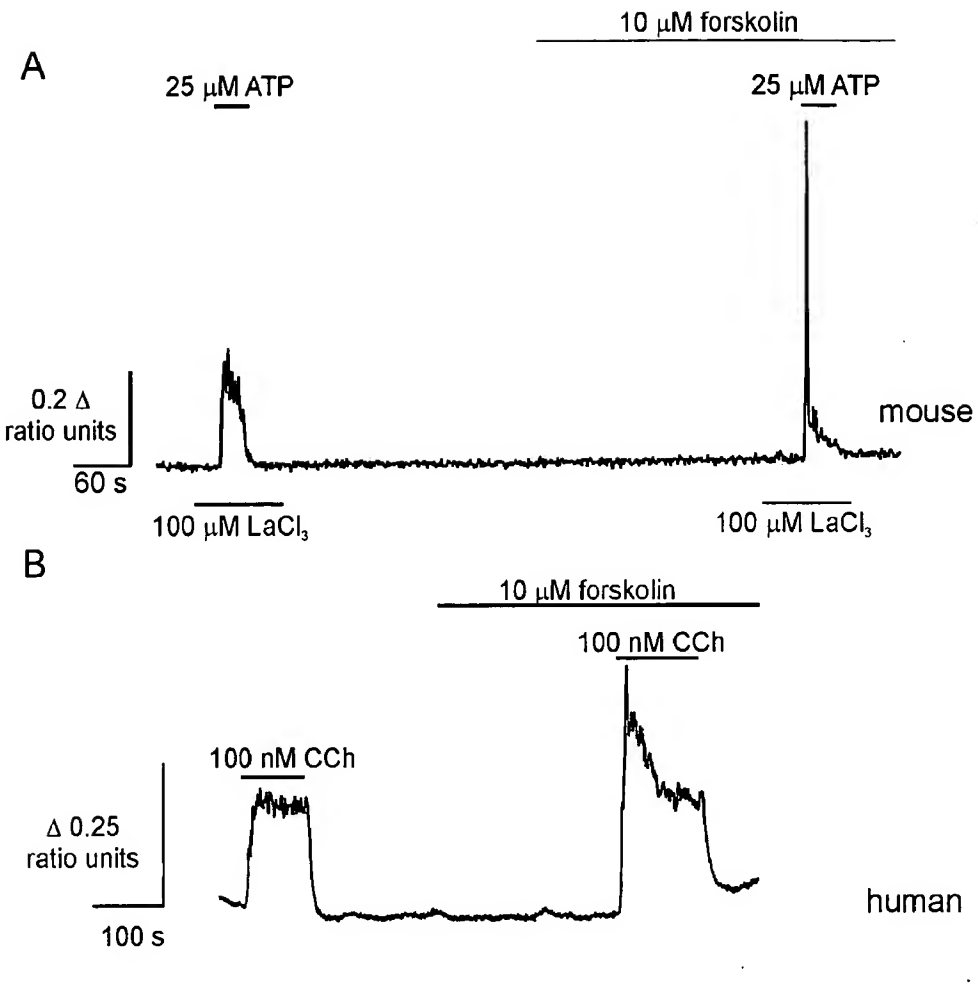
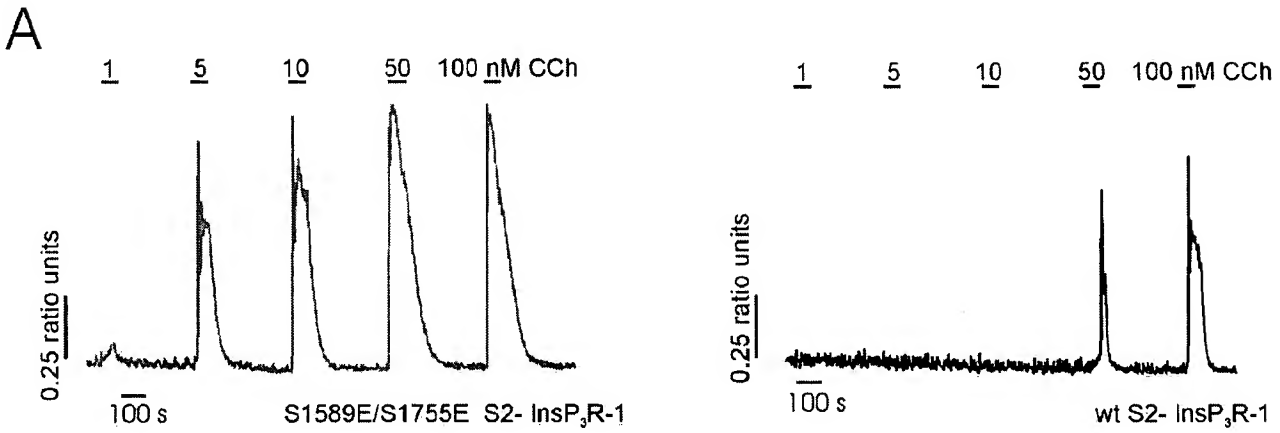

A
10 μM forskolin
25 μM ATP
25 μM ATP
0.2 Δ
ratio units
60 s
mouse
100 μM LaCl3
100 μM LaCl3
B
10 μM forskolin
100 nM CCh
100 nM CCh
Δ 0.25
ratio units
100 s
human

Figure 7


A
1
5
10
50
100 nM CCh
0.25 ratio units
100 s
S1589E/S1755E S2- InsP3R-1
1
5
10
50
100 nM CCh
0.25 ratio units
100 s
wt S2- InsP3R-1

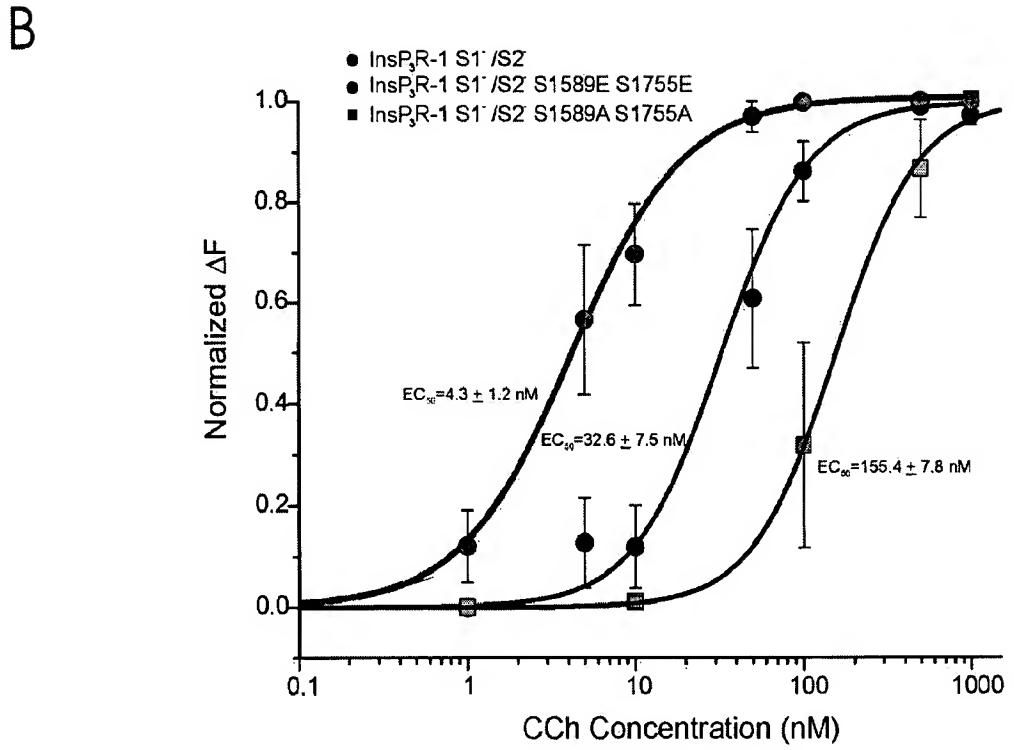

B
InsP3R-1 S1-/S2-
InsP3R-1 S1-/S2- S1589E S1755E
InsP3R-1 S1-/S2- S1589A S1755A
Normalized ΔF
1.0
0.8
0.6
0.4
0.2
0.0
EC50=4.3 ± 1.2 nM
EC50=32.6 ± 7.5 nM
EC50=155.4 ± 7.8 nM
0.1
1
10
100
1000
CCh Concentration (nM)

Figure 8

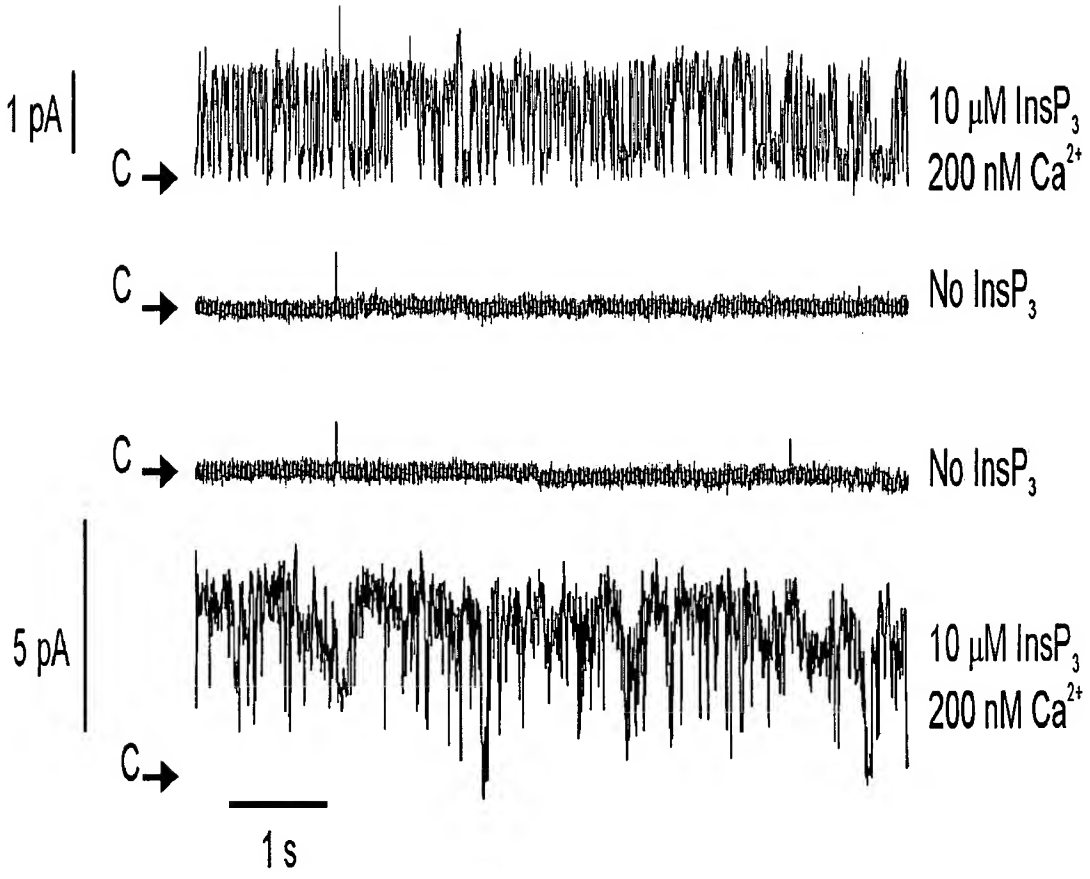
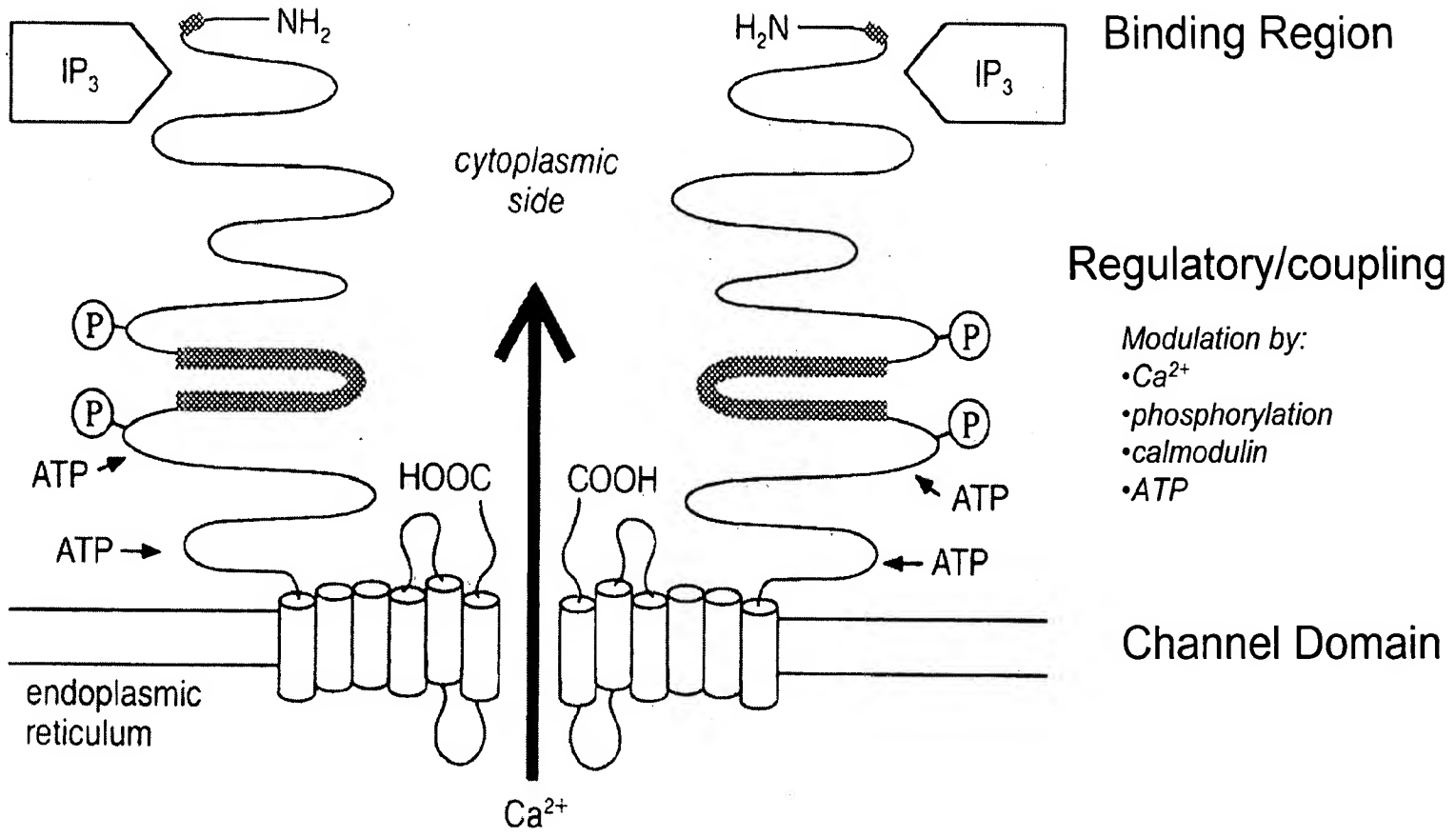

1 pA
C
10 μM InsP3
200 nM Ca2+
C
No InsP3
C
No InsP3
5 pA
10 μM InsP3
200 nM Ca2+
C
1 s

Figure 9



Adapted from Mikoshiba TIPs. 14(3):86-9, 1993

Figure 10

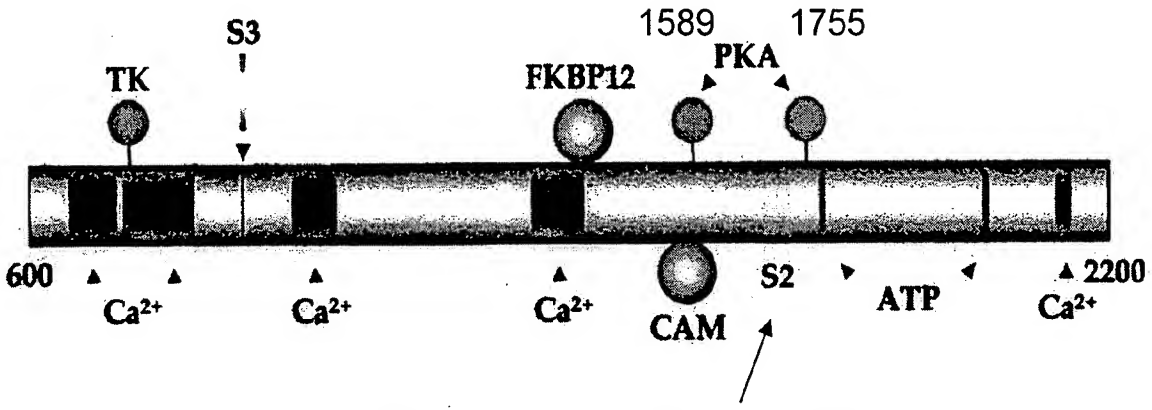

S3
1589
1755
TK
FKBP12
PKA
600
Ca2+
Ca2+
Ca2+
CAM
S2
ATP
2200
Ca2+
S2+=neuronal "long form"
S2-=peripheral "short form"

Figure 11

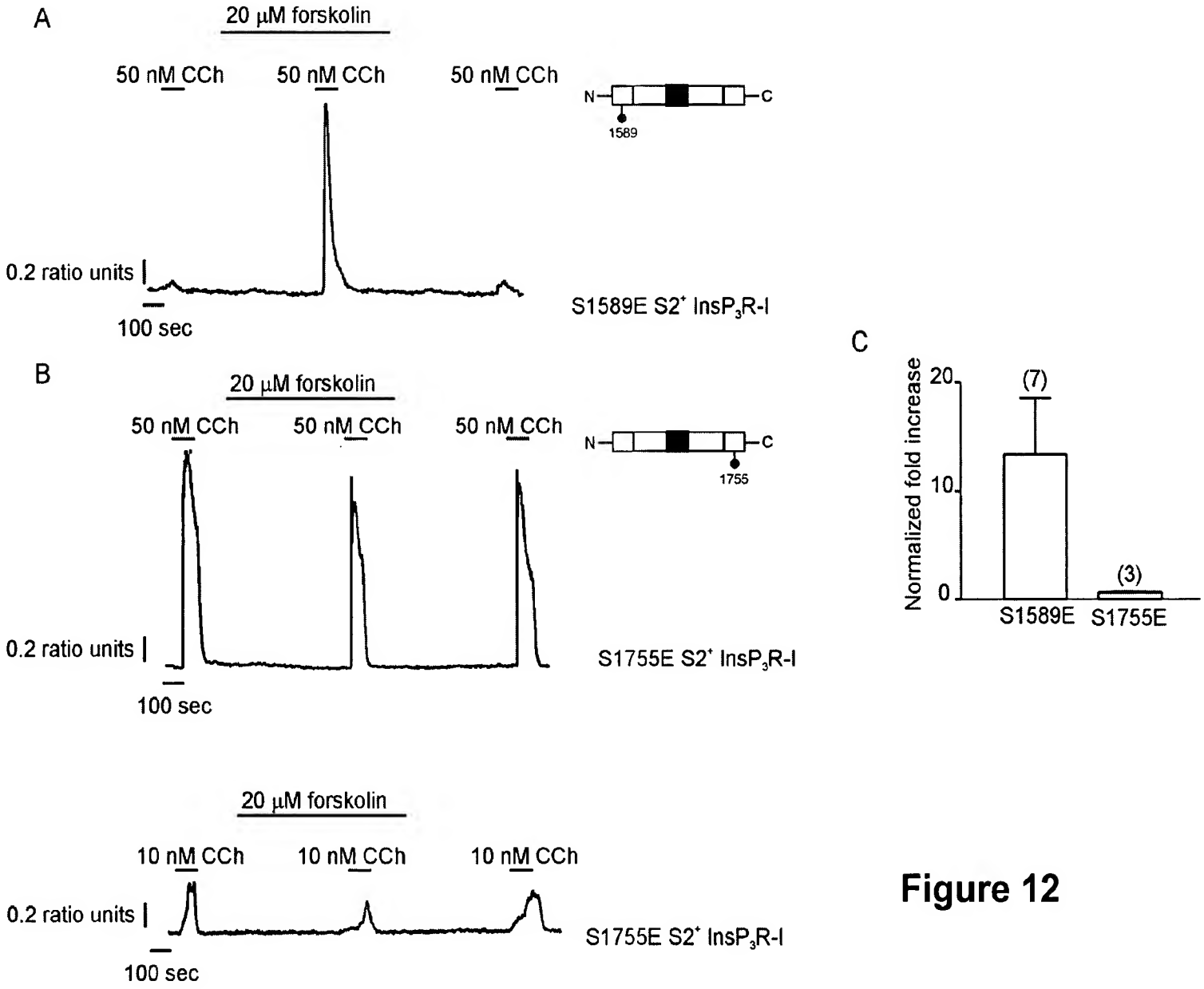

A
20 μM forskolin
50 nM CCh
50 nM CCh
50 nM CCh
N
C
1589
0.2 ratio units
100 sec
S1589E S2+ InsP3R-I
B
20 μM forskolin
50 nM CCh
50 nM CCh
50 nM CCh
N
C
1755
0.2 ratio units
100 sec
S1755E S2+ InsP3R-I
20 μM forskolin
10 nM CCh
10 nM CCh
10 nM CCh
0.2 ratio units
100 sec
S1755E S2+ InsP3R-I
C
Normalized fold increase
20
10
0
(7)
(3)
S1589E
S1755E

Figure 12

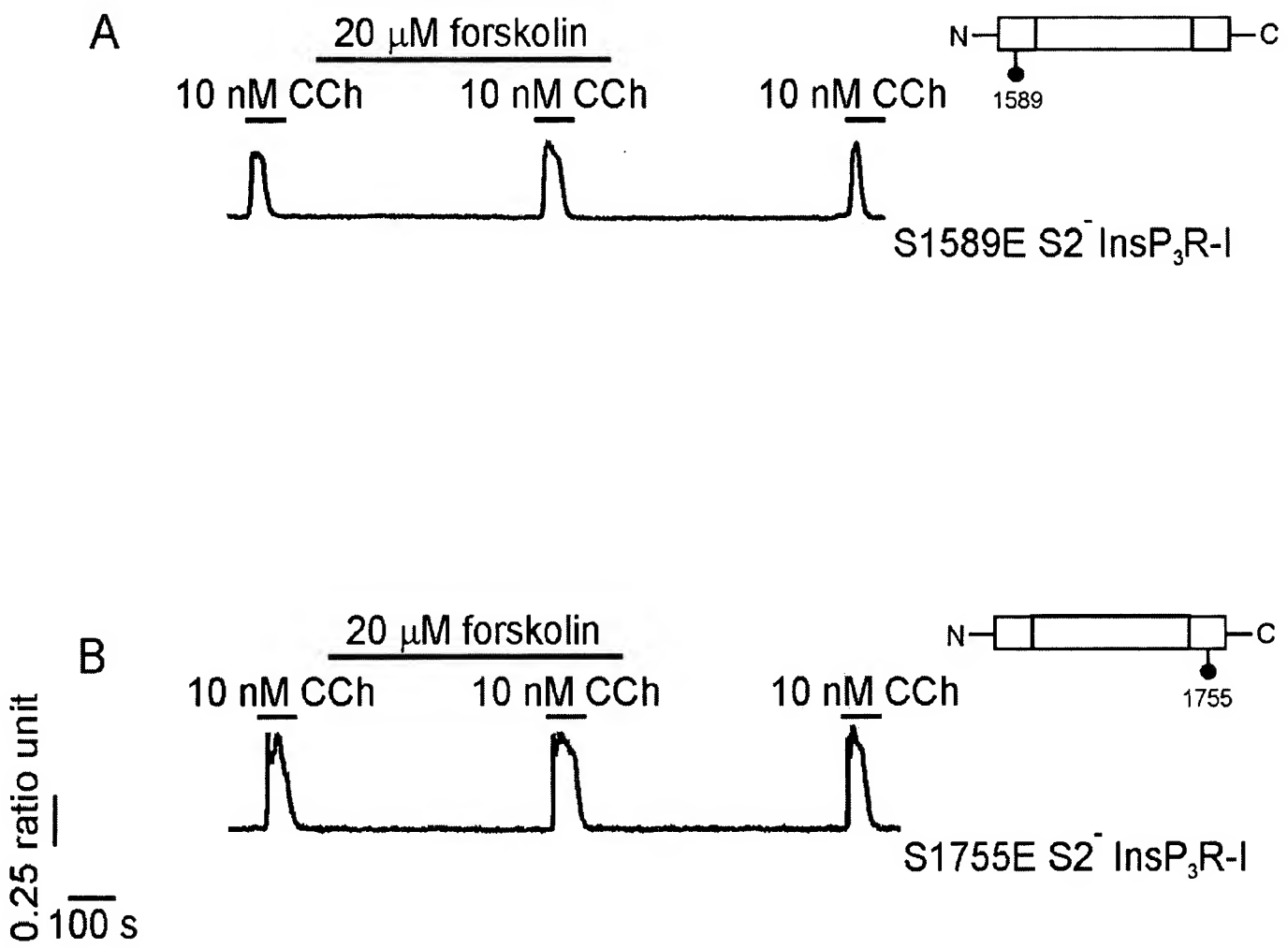

A
20 μM forskolin
10 nM CCh
10 nM CCh
10 nM CCh
N
C
1589
S1589E S2⁻ InsP3R-I
B
20 μM forskolin
10 nM CCh
10 nM CCh
10 nM CCh
N
C
1755
S1755E S2⁻ InsP3R-I
0.25 ratio unit
100 s

Figure 13

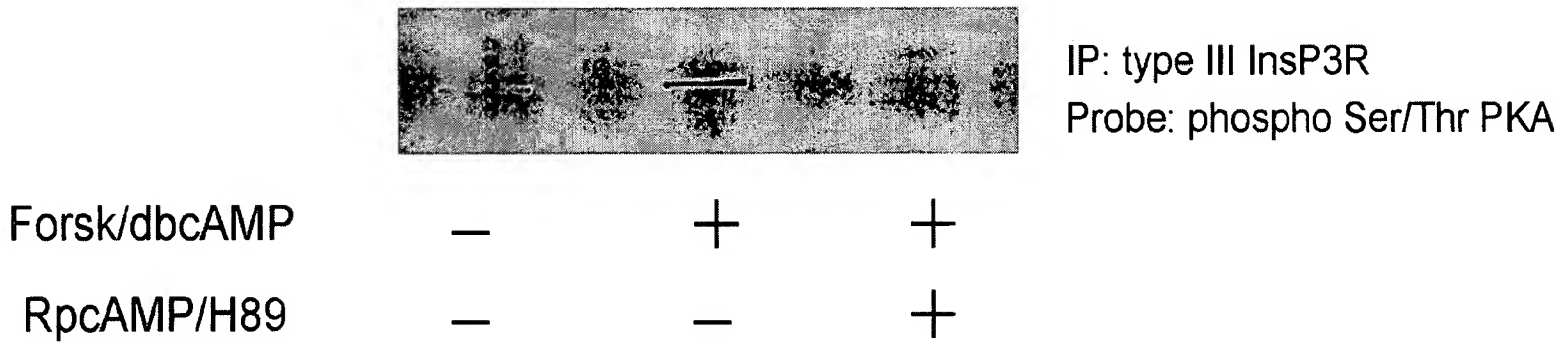

DT-40 IP3R-III cells
IP: type III InsP3R
Probe: phospho Ser/Thr PKA
Forsk/dbcAMP
RpcAMP/H89
–
+
+
–
–
+

Figure 14

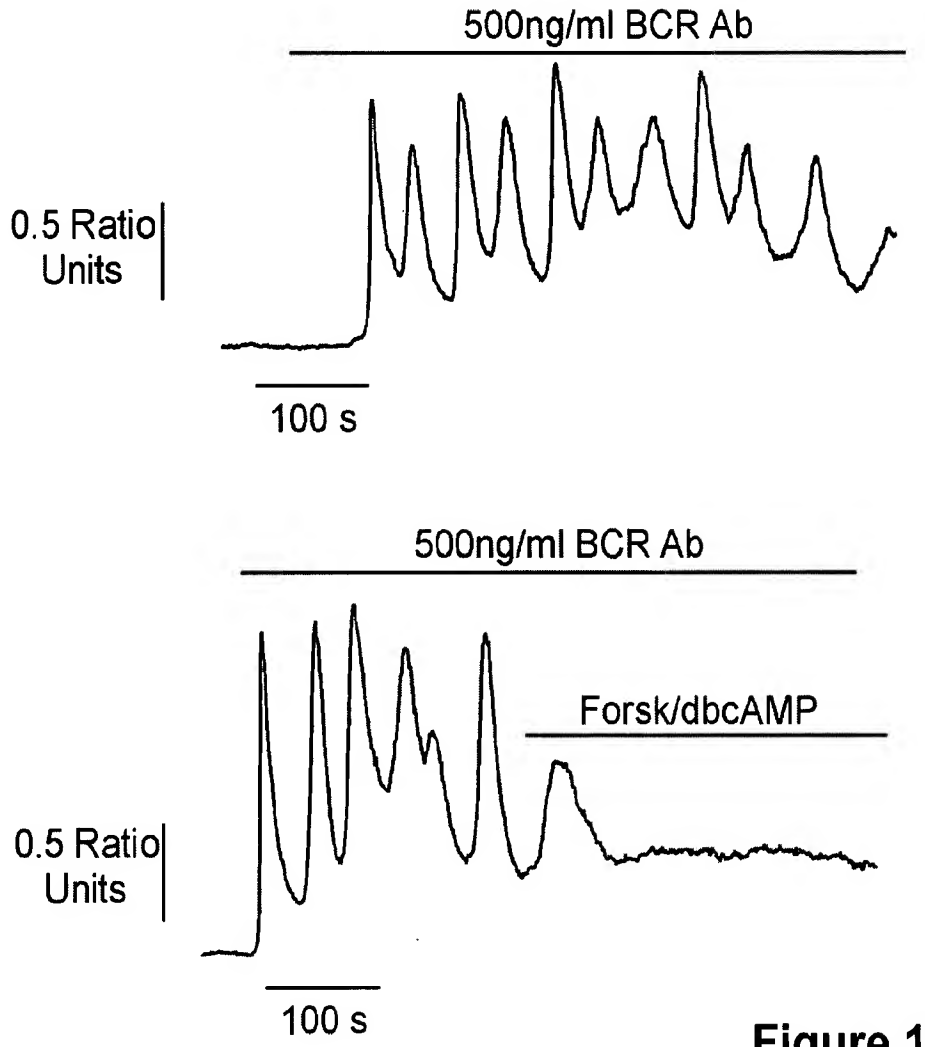
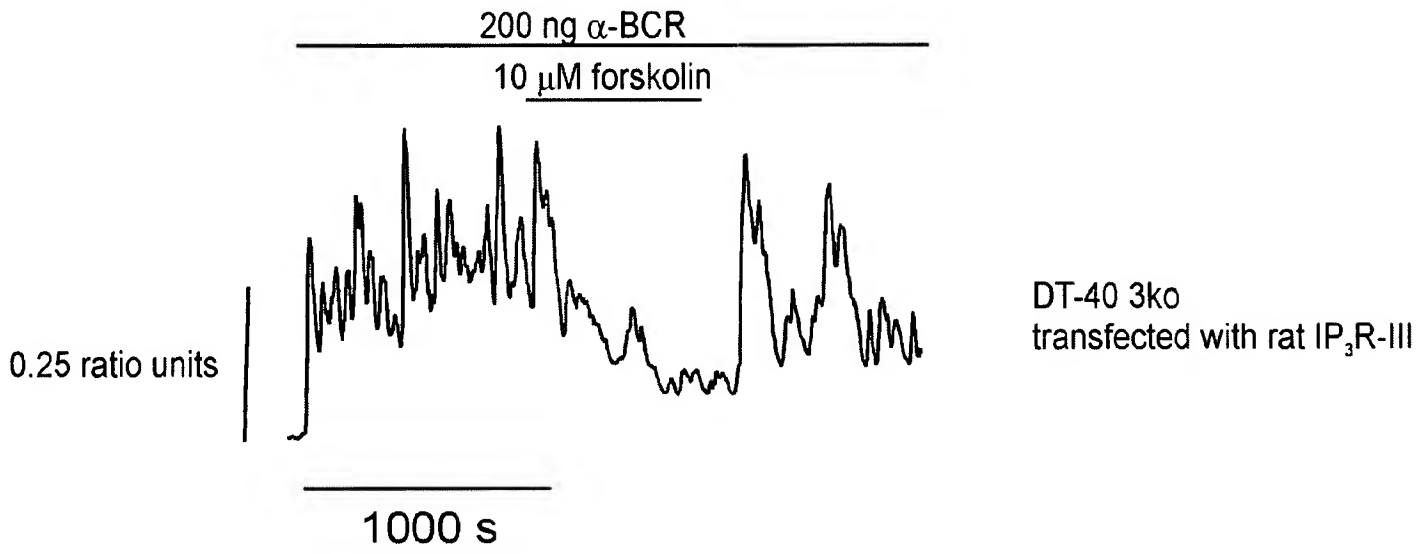

500ng/ml BCR Ab
0.5 Ratio Units
100 s
500ng/ml BCR Ab
Forsk/dbcAMP
0.5 Ratio Units
100 s

Figure 15


200 ng α-BCR
10 μM forskolin
0.25 ratio units
1000 s
DT-40 3ko
transfected with rat IP3R-III

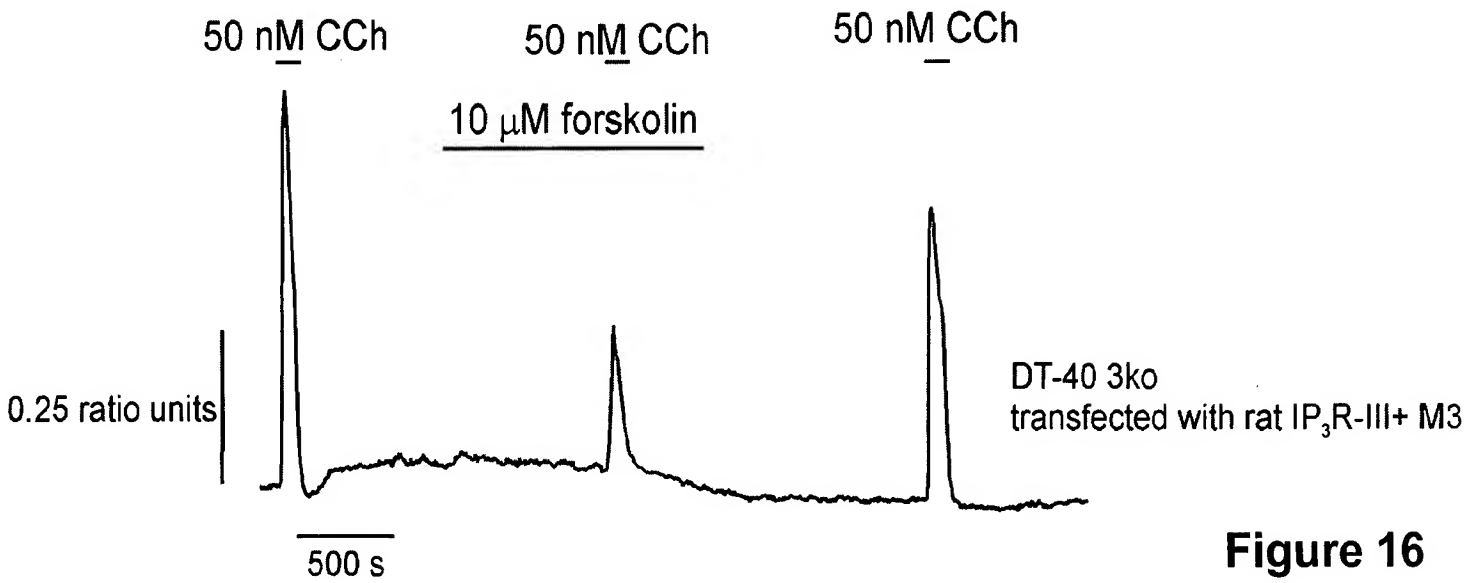

50 nM CCh
50 nM CCh
50 nM CCh
10 μM forskolin
0.25 ratio units
500 s
DT-40 3ko
transfected with rat IP3R-III+ M3

Figure 16

SEQUENCE LISTING

<110> Yule, D.I.
Wagner II, Larry

<120> Inositol 1,4,5-trisphosphate receptor mutants and uses thereof

<130> 21108.0042U1

<160> 22

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 2710
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/note = synthetic construct

<400> 1

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 1               5                  10                  15
Leu Tyr Ala Glu Gly Ser Thr Asn Gly Phe Ile Ser Thr Leu Gly Leu
            20                  25                  30
Val Asp Asp Arg Cys Val Val Gln Pro Glu Ala Gly Asp Leu Asn Asn
        35                  40                  45
Pro Pro Lys Lys Phe Arg Asp Cys Leu Phe Lys Leu Cys Pro Met Asn
    50                  55                  60
Arg Tyr Ser Ala Gln Lys Gln Phe Trp Lys Ala Ala Lys Pro Gly Ala
65                  70                  75                  80
Asn Ser Thr Thr Asp Ala Val Leu Leu Asn Lys Leu His His Ala Ala
                85                  90                  95
Asp Leu Glu Lys Lys Gln Asn Glu Thr Glu Asn Arg Lys Leu Leu Gly
            100                 105                 110
Thr Val Ile Gln Tyr Gly Asn Val Ile Gln Leu Leu His Leu Lys Ser
        115                 120                 125
Asn Lys Tyr Leu Thr Val Asn Lys Arg Leu Pro Ala Leu Leu Glu Lys
    130                 135                 140
Asn Ala Met Arg Val Thr Leu Asp Glu Ala Gly Asn Glu Gly Ser Trp
145                 150                 155                 160
Phe Tyr Ile Gln Pro Phe Tyr Lys Leu Arg Ser Ile Gly Asp Ser Val
                165                 170                 175
Val Ile Gly Asp Lys Val Val Leu Asn Pro Val Asn Ala Gly Gln Pro
            180                 185                 190
Leu His Ala Ser Ser His Gln Leu Val Asp Asn Pro Gly Cys Asn Glu
        195                 200                 205
Val Asn Ser Val Asn Cys Asn Thr Ser Trp Lys Ile Val Leu Phe Met
    210                 215                 220
Lys Trp Ser Asp Asn Lys Asp Asp Ile Leu Lys Gly Gly Asp Val Val
225                 230                 235                 240
Arg Leu Phe His Ala Glu Gln Glu Lys Phe Leu Thr Cys Asp Glu His
                245                 250                 255
Arg Lys Lys Gln His Val Phe Leu Arg Thr Thr Gly Arg Gln Ser Ala
            260                 265                 270
```

```
Thr Ser Ala Thr Ser Ser Lys Ala Leu Trp Glu Val Glu Val Val Gln
        275                 280                 285
His Asp Pro Cys Arg Gly Gly Ala Gly Tyr Trp Asn Ser Leu Phe Arg
    290                 295                 300
Phe Lys His Leu Ala Thr Gly His Tyr Leu Ala Ala Glu Val Asp Pro
305                 310                 315                 320
Asp Phe Glu Glu Glu Cys Leu Glu Phe Gln Pro Ser Val Asp Pro Asp
                325                 330                 335
Gln Asp Ala Ser Arg Ser Arg Leu Arg Asn Ala Gln Glu Lys Met Val
            340                 345                 350
Tyr Ser Leu Val Ser Val Pro Glu Gly Asn Asp Ile Ser Ser Ile Phe
        355                 360                 365
Glu Leu Asp Pro Thr Thr Leu Arg Gly Gly Asp Ser Leu Val Pro Arg
    370                 375                 380
Asn Ser Tyr Val Arg Leu Arg His Leu Cys Thr Asn Thr Trp Val His
385                 390                 395                 400
Ser Thr Asn Ile Pro Ile Asp Lys Glu Glu Glu Lys Pro Val Met Leu
                405                 410                 415
Lys Ile Gly Thr Ser Pro Leu Lys Glu Asp Lys Glu Ala Phe Ala Ile
            420                 425                 430
Val Pro Val Ser Pro Ala Glu Val Arg Asp Leu Asp Phe Ala Asn Asp
        435                 440                 445
Ala Ser Lys Val Leu Gly Ser Ile Ala Gly Lys Leu Glu Lys Gly Thr
    450                 455                 460
Ile Thr Gln Asn Glu Arg Arg Ser Val Thr Lys Leu Leu Glu Asp Leu
465                 470                 475                 480
Val Tyr Phe Val Thr Gly Gly Thr Asn Ser Gly Gln Asp Val Leu Glu
                485                 490                 495
Val Val Phe Ser Lys Pro Asn Arg Glu Arg Gln Lys Leu Met Arg Glu
            500                 505                 510
Gln Asn Ile Leu Lys Gln Ile Phe Lys Leu Leu Gln Ala Pro Phe Thr
        515                 520                 525
Asp Cys Gly Asp Gly Pro Met Leu Arg Leu Glu Glu Leu Gly Asp Gln
    530                 535                 540
Arg His Ala Pro Phe Arg His Ile Cys Arg Leu Cys Tyr Arg Val Leu
545                 550                 555                 560
Arg His Ser Gln Gln Asp Tyr Arg Lys Asn Gln Glu Tyr Ile Ala Lys
                565                 570                 575
Gln Phe Gly Phe Met Gln Lys Gln Ile Gly Tyr Asp Val Leu Ala Glu
            580                 585                 590
Asp Thr Ile Thr Ala Leu Leu His Asn Asn Arg Lys Leu Leu Glu Lys
        595                 600                 605
His Ile Thr Ala Ala Glu Ile Asp Thr Phe Val Ser Leu Val Arg Lys
    610                 615                 620
Asn Arg Glu Pro Arg Phe Leu Asp Tyr Leu Ser Asp Leu Cys Val Ser
625                 630                 635                 640
Met Asn Lys Ser Ile Pro Val Thr Gln Glu Leu Ile Cys Lys Ala Val
                645                 650                 655
Leu Asn Pro Thr Asn Ala Asp Ile Leu Ile Glu Thr Lys Leu Val Leu
            660                 665                 670
Ser Arg Phe Glu Phe Glu Gly Val Ser Thr Gly Glu Asn Ala Leu Glu
        675                 680                 685
Ala Gly Glu Asp Glu Glu Glu Val Trp Leu Phe Trp Arg Asp Ser Asn
    690                 695                 700
Lys Glu Ile Arg Ser Lys Ser Val Arg Glu Leu Ala Gln Asp Ala Lys
705                 710                 715                 720
Glu Gly Gln Lys Glu Asp Arg Asp Val Leu Ser Tyr Tyr Arg Tyr Gln
                725                 730                 735
Leu Asn Leu Phe Ala Arg Met Cys Leu Asp Arg Gln Tyr Leu Ala Ile
            740                 745                 750
```

```
Asn Glu Ile Ser Gly Gln Leu Asp Val Asp Leu Ile Leu Arg Cys Met
        755                 760                 765
Ser Asp Glu Asn Leu Pro Tyr Asp Leu Arg Ala Ser Phe Cys Arg Leu
    770                 775                 780
Met Leu His Met His Val Asp Arg Asp Pro Gln Glu Gln Val Thr Pro
785                 790                 795                 800
Val Lys Tyr Ala Arg Leu Trp Ser Glu Ile Pro Ser Glu Ile Ala Ile
                805                 810                 815
Asp Asp Tyr Asp Ser Ser Gly Ala Ser Lys Asp Glu Ile Lys Glu Arg
            820                 825                 830
Phe Ala Gln Thr Met Glu Phe Val Glu Glu Tyr Leu Arg Asp Val Val
        835                 840                 845
Cys Gln Arg Phe Pro Phe Ser Asp Lys Glu Lys Asn Lys Leu Thr Phe
    850                 855                 860
Glu Val Val Asn Leu Ala Arg Asn Leu Ile Tyr Phe Gly Phe Tyr Asn
865                 870                 875                 880
Phe Ser Asp Leu Leu Arg Leu Thr Lys Ile Leu Leu Ala Ile Leu Asp
                885                 890                 895
Cys Val His Val Thr Thr Ile Phe Pro Ile Ser Lys Met Thr Lys Gly
            900                 905                 910
Glu Glu Asn Lys Gly Ser Asn Val Met Arg Ser Ile His Gly Val Gly
        915                 920                 925
Glu Leu Met Thr Gln Val Val Leu Arg Gly Gly Gly Phe Leu Pro Met
    930                 935                 940
Thr Pro Met Ala Ala Ala Pro Glu Gly Asn Val Lys Gln Ala Glu Pro
945                 950                 955                 960
Glu Lys Glu Asp Ile Met Val Met Asp Thr Lys Leu Lys Ile Ile Glu
                965                 970                 975
Ile Leu Gln Phe Ile Leu Asn Val Arg Leu Asp Tyr Arg Ile Ser Cys
            980                 985                 990
Leu Leu Cys Ile Phe Lys Arg Glu Phe Asp Glu Ser Asn Ser Gln Ser
        995                 1000                1005
Ser Glu Thr Ser Ser Gly Asn Ser Ser Gln Glu Gly Pro Ser Asn Val
    1010                1015                1020
Pro Gly Ala Leu Asp Phe Glu His Ile Glu Glu Gln Ala Glu Gly Ile
1025                1030                1035                1040
Phe Gly Gly Ser Glu Glu Asn Thr Pro Leu Asp Leu Asp Asp His Gly
                1045                1050                1055
Gly Arg Thr Phe Leu Arg Val Leu Leu His Leu Thr Met His Asp Tyr
            1060                1065                1070
Pro Pro Leu Val Ser Gly Ala Leu Gln Leu Leu Phe Arg His Phe Ser
        1075                1080                1085
Gln Arg Gln Glu Val Leu Gln Ala Phe Lys Gln Val Gln Leu Leu Val
    1090                1095                1100
Thr Ser Gln Asp Val Asp Asn Tyr Lys Gln Ile Lys Gln Asp Leu Asp
1105                1110                1115                1120
Gln Leu Arg Ser Ile Val Glu Lys Ser Glu Leu Trp Val Tyr Lys Gly
                1125                1130                1135
Gln Gly Pro Asp Glu Pro Met Asp Gly Ala Ser Gly Glu Asn Glu His
            1140                1145                1150
Lys Lys Thr Glu Glu Gly Thr Ser Lys Pro Leu Lys His Glu Ser Thr
        1155                1160                1165
Ser Ser Tyr Asn Tyr Arg Val Val Lys Glu Ile Leu Ile Arg Leu Ser
    1170                1175                1180
Lys Leu Cys Val Gln Glu Ser Ala Ser Val Arg Lys Ser Arg Lys Gln
1185                1190                1195                1200
Gln Gln Arg Leu Leu Arg Asn Met Gly Ala His Ala Val Val Leu Glu
                1205                1210                1215
Leu Leu Gln Ile Pro Tyr Glu Lys Ala Glu Asp Thr Lys Met Gln Glu
            1220                1225                1230
```

```
Ile Met Arg Leu Ala His Glu Phe Leu Gln Asn Phe Cys Ala Gly Asn
        1235                1240                1245
Gln Gln Asn Gln Ala Leu Leu His Lys His Ile Asn Leu Phe Leu Asn
    1250                1255                1260
Pro Gly Ile Leu Glu Ala Val Thr Met Gln His Ile Phe Met Asn Asn
1265                1270                1275                1280
Phe Gln Leu Cys Ser Glu Ile Asn Glu Arg Val Val Gln His Phe Val
                1285                1290                1295
His Cys Ile Glu Thr His Gly Arg Asn Val Gln Tyr Ile Lys Phe Leu
            1300                1305                1310
Gln Thr Ile Val Lys Ala Glu Gly Lys Phe Ile Lys Lys Cys Gln Asp
        1315                1320                1325
Met Val Met Ala Glu Leu Val Asn Ser Gly Glu Asp Val Leu Val Phe
    1330                1335                1340
Tyr Asn Asp Arg Ala Ser Phe Gln Thr Leu Ile Gln Met Met Arg Ser
1345                1350                1355                1360
Glu Arg Asp Arg Met Asp Glu Asn Ser Pro Leu Phe Met Tyr His Ile
                1365                1370                1375
His Leu Val Glu Leu Leu Ala Val Cys Thr Glu Gly Lys Asn Val Tyr
            1380                1385                1390
Thr Glu Ile Lys Cys Asn Ser Leu Leu Pro Leu Asp Asp Ile Val Arg
        1395                1400                1405
Val Val Thr His Glu Asp Cys Ile Pro Glu Val Lys Ile Ala Tyr Ile
    1410                1415                1420
Asn Phe Leu Asn His Cys Tyr Val Asp Thr Glu Val Glu Met Lys Glu
1425                1430                1435                1440
Ile Tyr Thr Ser Asn His Met Trp Lys Leu Phe Glu Asn Phe Leu Val
                1445                1450                1455
Asp Ile Cys Arg Ala Cys Asn Asn Thr Ser Asp Arg Lys His Ala Asp
            1460                1465                1470
Ser Val Leu Glu Lys Tyr Val Thr Glu Ile Val Met Ser Ile Val Thr
        1475                1480                1485
Thr Phe Phe Ser Ser Pro Phe Ser Asp Gln Ser Thr Thr Leu Gln Thr
    1490                1495                1500
Arg Gln Pro Val Phe Val Gln Leu Leu Gln Gly Val Phe Arg Val Tyr
1505                1510                1515                1520
His Cys Asn Trp Leu Met Pro Ser Gln Lys Ala Ser Val Glu Ser Cys
                1525                1530                1535
Ile Arg Val Leu Ser Asp Val Ala Lys Ser Arg Ala Ile Ala Ile Pro
            1540                1545                1550
Val Asp Leu Asp Ser Gln Val Asn Asn Leu Phe Leu Lys Ser His Asn
        1555                1560                1565
Ile Val Gln Lys Thr Ala Met Asn Trp Arg Leu Ser Ala Arg Asn Ala
    1570                1575                1580
Ala Arg Arg Asp Glu Val Leu Ala Ala Ser Arg Asp Tyr Arg Asn Ile
1585                1590                1595                1600
Ile Glu Arg Leu Gln Asp Ile Val Ser Ala Leu Glu Asp Arg Leu Arg
                1605                1610                1615
Pro Leu Val Gln Ala Glu Leu Ser Val Leu Val Asp Val Leu His Arg
            1620                1625                1630
Pro Glu Leu Leu Phe Pro Glu Asn Thr Asp Ala Arg Arg Lys Cys Glu
        1635                1640                1645
Ser Gly Gly Phe Ile Cys Lys Leu Ile Lys His Thr Lys Gln Leu Leu
    1650                1655                1660
Glu Glu Asn Glu Glu Lys Leu Cys Ile Lys Val Leu Gln Thr Leu Arg
1665                1670                1675                1680
Glu Met Met Thr Lys Asp Arg Gly Tyr Gly Glu Lys Gly Glu Ala Leu
                1685                1690                1695
Arg Gln Ile Leu Val Asn Arg Tyr Tyr Gly Asn Ile Arg Pro Ser Gly
            1700                1705                1710
```

```
Arg Arg Glu Ser Leu Thr Ser Phe Gly Asn Gly Pro Leu Ser Pro Gly
        1715                1720                1725
Gly Pro Ser Lys Pro Gly Gly Gly Gly Gly Gly Pro Gly Ser Gly Ser
    1730                1735                1740
Thr Ser Arg Gly Glu Met Ser Leu Ala Glu Val Gln Cys His Leu Asp
1745                1750                1755                1760
Lys Glu Gly Ala Ser Asn Leu Val Ile Asp Leu Ile Met Asn Ala Ser
                1765                1770                1775
Ser Asp Arg Val Phe His Glu Ser Ile Leu Leu Ala Ile Ala Leu Leu
            1780                1785                1790
Glu Gly Gly Asn Thr Thr Ile Gln His Ser Phe Phe Cys Arg Leu Thr
        1795                1800                1805
Glu Asp Lys Lys Ser Glu Lys Phe Phe Lys Val Phe Tyr Asp Arg Met
    1810                1815                1820
Lys Val Ala Gln Gln Glu Ile Lys Ala Thr Val Thr Val Asn Thr Ser
1825                1830                1835                1840
Asp Leu Gly Asn Lys Lys Lys Asp Asp Glu Val Asp Arg Asp Ala Pro
                1845                1850                1855
Ser Arg Lys Lys Ala Lys Glu Pro Thr Thr Gln Ile Thr Glu Glu Val
            1860                1865                1870
Arg Asp Gln Leu Leu Glu Ala Ser Ala Ala Thr Arg Lys Ala Phe Thr
        1875                1880                1885
Thr Phe Arg Arg Glu Ala Asp Pro Asp Asp His Tyr Gln Ser Gly Glu
    1890                1895                1900
Gly Thr Gln Ala Thr Thr Asp Lys Ala Lys Asp Asp Leu Glu Met Ser
1905                1910                1915                1920
Ala Val Ile Thr Ile Met Gln Pro Ile Leu Arg Phe Leu Gln Leu Leu
                1925                1930                1935
Cys Glu Asn His Asn Arg Asp Leu Gln Asn Phe Leu Arg Cys Gln Asn
            1940                1945                1950
Asn Lys Thr Asn Tyr Asn Leu Val Cys Glu Thr Leu Gln Phe Leu Asp
        1955                1960                1965
Cys Ile Cys Gly Ser Thr Thr Gly Gly Leu Gly Leu Leu Gly Leu Tyr
    1970                1975                1980
Ile Asn Glu Lys Asn Val Ala Leu Ile Asn Gln Thr Leu Glu Ser Leu
1985                1990                1995                2000
Thr Glu Tyr Cys Gln Gly Pro Cys His Glu Asn Gln Asn Cys Ile Ala
                2005                2010                2015
Thr His Glu Ser Asn Gly Ile Asp Ile Ile Thr Ala Leu Ile Leu Asn
            2020                2025                2030
Asp Ile Asn Pro Leu Gly Lys Lys Arg Met Asp Leu Val Leu Glu Leu
        2035                2040                2045
Lys Asn Asn Ala Ser Lys Leu Leu Leu Ala Ile Met Glu Ser Arg His
    2050                2055                2060
Asp Ser Glu Asn Ala Glu Arg Ile Leu Tyr Asn Met Arg Pro Lys Glu
2065                2070                2075                2080
Leu Val Glu Val Ile Lys Lys Ala Tyr Met Gln Gly Glu Val Glu Phe
                2085                2090                2095
Glu Asp Gly Glu Asn Gly Glu Asp Gly Ala Ala Ser Pro Arg Asn Val
            2100                2105                2110
Gly His Asn Ile Tyr Ile Leu Ala His Gln Leu Ala Arg His Asn Lys
        2115                2120                2125
Glu Leu Gln Thr Met Leu Lys Pro Gly Gly Gln Val Asp Gly Asp Glu
    2130                2135                2140
Ala Leu Glu Phe Tyr Ala Lys His Thr Ala Gln Ile Glu Ile Val Arg
2145                2150                2155                2160
Leu Asp Arg Thr Met Glu Gln Ile Val Phe Pro Val Pro Ser Ile Cys
                2165                2170                2175
Glu Phe Leu Thr Lys Glu Ser Lys Leu Arg Ile Tyr Tyr Thr Thr Glu
            2180                2185                2190
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Arg Asp Glu Gln Gly Ser Lys Ile Asn Asp Phe Phe Leu Arg Ser Glu
        2195                2200                2205
Asp Leu Phe Asn Glu Met Asn Trp Gln Lys Lys Leu Arg Ala Gln Pro
    2210                2215                2220
Val Leu Tyr Trp Cys Ala Arg Asn Met Ser Phe Trp Ser Ser Ile Ser
2225                2230                2235                2240
Phe Asn Leu Ala Val Leu Met Asn Leu Leu Val Ala Phe Phe Tyr Pro
                2245                2250                2255
Phe Lys Gly Val Arg Gly Gly Thr Leu Glu Pro His Trp Ser Gly Leu
            2260                2265                2270
Leu Trp Thr Ala Met Leu Ile Ser Leu Ala Ile Val Ile Ala Leu Pro
        2275                2280                2285
Lys Pro His Gly Ile Arg Ala Leu Ile Ala Ser Thr Ile Leu Arg Leu
    2290                2295                2300
Ile Phe Ser Val Gly Leu Gln Pro Thr Leu Phe Leu Leu Gly Ala Phe
2305                2310                2315                2320
Asn Val Cys Asn Lys Ile Ile Phe Leu Met Ser Phe Val Gly Asn Cys
                2325                2330                2335
Gly Thr Phe Thr Arg Gly Tyr Arg Ala Met Val Leu Asp Val Glu Phe
            2340                2345                2350
Leu Tyr His Leu Leu Tyr Leu Leu Ile Cys Ala Met Gly Leu Phe Val
        2355                2360                2365
His Glu Phe Phe Tyr Ser Leu Leu Leu Phe Asp Leu Val Tyr Arg Glu
    2370                2375                2380
Glu Thr Leu Leu Asn Val Ile Lys Ser Val Thr Arg Asn Gly Arg Pro
2385                2390                2395                2400
Ile Ile Leu Thr Ala Ala Leu Ala Leu Ile Leu Val Tyr Leu Phe Ser
                2405                2410                2415
Ile Val Gly Tyr Leu Phe Phe Lys Asp Asp Phe Ile Leu Glu Val Asp
            2420                2425                2430
Arg Leu Pro Asn Glu Thr Ala Gly Pro Glu Thr Gly Glu Ser Leu Ala
        2435                2440                2445
Asn Asp Phe Leu Tyr Ser Asp Val Cys Arg Val Glu Thr Gly Glu Asn
    2450                2455                2460
Cys Thr Ser Pro Ala Pro Lys Glu Glu Leu Leu Pro Val Glu Glu Thr
2465                2470                2475                2480
Glu Gln Asp Lys Glu His Thr Cys Glu Thr Leu Leu Met Cys Ile Val
                2485                2490                2495
Thr Val Leu Ser His Gly Leu Arg Ser Gly Gly Gly Val Gly Asp Val
            2500                2505                2510
Leu Arg Lys Pro Ser Lys Glu Glu Pro Leu Phe Ala Ala Arg Val Ile
        2515                2520                2525
Tyr Asp Leu Leu Phe Phe Phe Met Val Ile Ile Ile Val Leu Asn Leu
    2530                2535                2540
Ile Phe Gly Val Ile Ile Asp Thr Phe Ala Asp Leu Arg Ser Glu Lys
2545                2550                2555                2560
Gln Lys Lys Glu Glu Ile Leu Lys Thr Thr Cys Phe Ile Cys Gly Leu
                2565                2570                2575
Glu Arg Asp Lys Phe Asp Asn Lys Thr Val Thr Phe Glu Glu His Ile
            2580                2585                2590
Lys Glu Glu His Asn Met Trp His Tyr Leu Cys Phe Ile Val Leu Val
        2595                2600                2605
Lys Val Lys Asp Ser Thr Glu Tyr Thr Gly Pro Glu Ser Tyr Val Ala
    2610                2615                2620
Glu Met Ile Arg Glu Arg Asn Leu Asp Trp Phe Pro Arg Met Arg Ala
2625                2630                2635                2640
Met Ser Leu Val Ser Ser Asp Ser Glu Gly Glu Gln Asn Glu Leu Arg
                2645                2650                2655
Asn Leu Gln Glu Lys Leu Glu Ser Thr Met Lys Leu Val Thr Asn Leu
            2660                2665                2670
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Ser Gly Gln Leu Ser Glu Leu Lys Asp Gln Met Thr Glu Gln Arg Lys
        2675                2680                2685
Gln Lys Gln Arg Ile Gly Leu Leu Gly His Pro Pro His Met Asn Val
    2690                2695                2700
Asn Pro Gln Gln Pro Ala
2705                2710


<210> 2
<211> 2749
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/note =
      synthetic construct

<400> 2
Met Ser Asp Lys Met Ser Ser Phe Leu His Ile Gly Asp Ile Cys Ser
 1               5                  10                  15
Leu Tyr Ala Glu Gly Ser Thr Asn Gly Phe Ile Ser Thr Leu Gly Leu
            20                  25                  30
Val Asp Asp Arg Cys Val Val Gln Pro Glu Ala Gly Asp Leu Asn Asn
        35                  40                  45
Pro Pro Lys Lys Phe Arg Asp Cys Leu Phe Lys Leu Cys Pro Met Asn
    50                  55                  60
Arg Tyr Ser Ala Gln Lys Gln Phe Trp Lys Ala Ala Lys Pro Gly Ala
65                  70                  75                  80
Asn Ser Thr Thr Asp Ala Val Leu Leu Asn Lys Leu His His Ala Ala
                85                  90                  95
Asp Leu Glu Lys Lys Gln Asn Glu Thr Glu Asn Arg Lys Leu Leu Gly
            100                 105                 110
Thr Val Ile Gln Tyr Gly Asn Val Ile Gln Leu Leu His Leu Lys Ser
        115                 120                 125
Asn Lys Tyr Leu Thr Val Asn Lys Arg Leu Pro Ala Leu Leu Glu Lys
    130                 135                 140
Asn Ala Met Arg Val Thr Leu Asp Glu Ala Gly Asn Glu Gly Ser Trp
145                 150                 155                 160
Phe Tyr Ile Gln Pro Phe Tyr Lys Leu Arg Ser Ile Gly Asp Ser Val
                165                 170                 175
Val Ile Gly Asp Lys Val Val Leu Asn Pro Val Asn Ala Gly Gln Pro
            180                 185                 190
Leu His Ala Ser Ser His Gln Leu Val Asp Asn Pro Gly Cys Asn Glu
        195                 200                 205
Val Asn Ser Val Asn Cys Asn Thr Ser Trp Lys Ile Val Leu Phe Met
    210                 215                 220
Lys Trp Ser Asp Asn Lys Asp Asp Ile Leu Lys Gly Gly Asp Val Val
225                 230                 235                 240
Arg Leu Phe His Ala Glu Gln Glu Lys Phe Leu Thr Cys Asp Glu His
                245                 250                 255
Arg Lys Lys Gln His Val Phe Leu Arg Thr Thr Gly Arg Gln Ser Ala
            260                 265                 270
Thr Ser Ala Thr Ser Ser Lys Ala Leu Trp Glu Val Glu Val Val Gln
        275                 280                 285
His Asp Pro Cys Arg Gly Gly Ala Gly Tyr Trp Asn Ser Leu Phe Arg
    290                 295                 300
Phe Lys His Leu Ala Thr Gly His Tyr Leu Ala Ala Glu Val Asp Pro
305                 310                 315                 320
Asp Phe Glu Glu Glu Cys Leu Glu Phe Gln Pro Ser Val Asp Pro Asp
                325                 330                 335
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Gln Asp Ala Ser Arg Ser Arg Leu Arg Asn Ala Gln Glu Lys Met Val
            340                 345                 350
Tyr Ser Leu Val Ser Val Pro Glu Gly Asn Asp Ile Ser Ser Ile Phe
        355                 360                 365
Glu Leu Asp Pro Thr Thr Leu Arg Gly Gly Asp Ser Leu Val Pro Arg
    370                 375                 380
Asn Ser Tyr Val Arg Leu Arg His Leu Cys Thr Asn Thr Trp Val His
385                 390                 395                 400
Ser Thr Asn Ile Pro Ile Asp Lys Glu Glu Glu Lys Pro Val Met Leu
                405                 410                 415
Lys Ile Gly Thr Ser Pro Leu Lys Glu Asp Lys Glu Ala Phe Ala Ile
            420                 425                 430
Val Pro Val Ser Pro Ala Glu Val Arg Asp Leu Asp Phe Ala Asn Asp
        435                 440                 445
Ala Ser Lys Val Leu Gly Ser Ile Ala Gly Lys Leu Glu Lys Gly Thr
    450                 455                 460
Ile Thr Gln Asn Glu Arg Arg Ser Val Thr Lys Leu Leu Glu Asp Leu
465                 470                 475                 480
Val Tyr Phe Val Thr Gly Gly Thr Asn Ser Gly Gln Asp Val Leu Glu
                485                 490                 495
Val Val Phe Ser Lys Pro Asn Arg Glu Arg Gln Lys Leu Met Arg Glu
            500                 505                 510
Gln Asn Ile Leu Lys Gln Ile Phe Lys Leu Leu Gln Ala Pro Phe Thr
        515                 520                 525
Asp Cys Gly Asp Gly Pro Met Leu Arg Leu Glu Glu Leu Gly Asp Gln
    530                 535                 540
Arg His Ala Pro Phe Arg His Ile Cys Arg Leu Cys Tyr Arg Val Leu
545                 550                 555                 560
Arg His Ser Gln Gln Asp Tyr Arg Lys Asn Gln Glu Tyr Ile Ala Lys
                565                 570                 575
Gln Phe Gly Phe Met Gln Lys Gln Ile Gly Tyr Asp Val Leu Ala Glu
            580                 585                 590
Asp Thr Ile Thr Ala Leu Leu His Asn Asn Arg Lys Leu Leu Glu Lys
        595                 600                 605
His Ile Thr Ala Ala Glu Ile Asp Thr Phe Val Ser Leu Val Arg Lys
    610                 615                 620
Asn Arg Glu Pro Arg Phe Leu Asp Tyr Leu Ser Asp Leu Cys Val Ser
625                 630                 635                 640
Met Asn Lys Ser Ile Pro Val Thr Gln Glu Leu Ile Cys Lys Ala Val
                645                 650                 655
Leu Asn Pro Thr Asn Ala Asp Ile Leu Ile Glu Thr Lys Leu Val Leu
            660                 665                 670
Ser Arg Phe Glu Phe Glu Gly Val Ser Thr Gly Glu Asn Ala Leu Glu
        675                 680                 685
Ala Gly Glu Asp Glu Glu Glu Val Trp Leu Phe Trp Arg Asp Ser Asn
    690                 695                 700
Lys Glu Ile Arg Ser Lys Ser Val Arg Glu Leu Ala Gln Asp Ala Lys
705                 710                 715                 720
Glu Gly Gln Lys Glu Asp Arg Asp Val Leu Ser Tyr Tyr Arg Tyr Gln
                725                 730                 735
Leu Asn Leu Phe Ala Arg Met Cys Leu Asp Arg Gln Tyr Leu Ala Ile
            740                 745                 750
Asn Glu Ile Ser Gly Gln Leu Asp Val Asp Leu Ile Leu Arg Cys Met
        755                 760                 765
Ser Asp Glu Asn Leu Pro Tyr Asp Leu Arg Ala Ser Phe Cys Arg Leu
    770                 775                 780
Met Leu His Met His Val Asp Arg Asp Pro Gln Glu Gln Val Thr Pro
785                 790                 795                 800
Val Lys Tyr Ala Arg Leu Trp Ser Glu Ile Pro Ser Glu Ile Ala Ile
                805                 810                 815
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Asp Asp Tyr Asp Ser Ser Gly Ala Ser Lys Asp Glu Ile Lys Glu Arg
            820                 825                 830
Phe Ala Gln Thr Met Glu Phe Val Glu Glu Tyr Leu Arg Asp Val Val
        835                 840                 845
Cys Gln Arg Phe Pro Phe Ser Asp Lys Glu Lys Asn Lys Leu Thr Phe
    850                 855                 860
Glu Val Val Asn Leu Ala Arg Asn Leu Ile Tyr Phe Gly Phe Tyr Asn
865                 870                 875                 880
Phe Ser Asp Leu Leu Arg Leu Thr Lys Ile Leu Leu Ala Ile Leu Asp
                885                 890                 895
Cys Val His Val Thr Thr Ile Phe Pro Ile Ser Lys Met Thr Lys Gly
            900                 905                 910
Glu Glu Asn Lys Gly Ser Asn Val Met Arg Ser Ile His Gly Val Gly
        915                 920                 925
Glu Leu Met Thr Gln Val Val Leu Arg Gly Gly Gly Phe Leu Pro Met
    930                 935                 940
Thr Pro Met Ala Ala Ala Pro Glu Gly Asn Val Lys Gln Ala Glu Pro
945                 950                 955                 960
Glu Lys Glu Asp Ile Met Val Met Asp Thr Lys Leu Lys Ile Ile Glu
                965                 970                 975
Ile Leu Gln Phe Ile Leu Asn Val Arg Leu Asp Tyr Arg Ile Ser Cys
            980                 985                 990
Leu Leu Cys Ile Phe Lys Arg Glu Phe Asp Glu Ser Asn Ser Gln Ser
        995                 1000                1005
Ser Glu Thr Ser Ser Gly Asn Ser Ser Gln Glu Gly Pro Ser Asn Val
    1010                1015                1020
Pro Gly Ala Leu Asp Phe Glu His Ile Glu Glu Gln Ala Glu Gly Ile
1025                1030                1035                1040
Phe Gly Gly Ser Glu Glu Asn Thr Pro Leu Asp Leu Asp Asp His Gly
                1045                1050                1055
Gly Arg Thr Phe Leu Arg Val Leu Leu His Leu Thr Met His Asp Tyr
            1060                1065                1070
Pro Pro Leu Val Ser Gly Ala Leu Gln Leu Leu Phe Arg His Phe Ser
        1075                1080                1085
Gln Arg Gln Glu Val Leu Gln Ala Phe Lys Gln Val Gln Leu Leu Val
    1090                1095                1100
Thr Ser Gln Asp Val Asp Asn Tyr Lys Gln Ile Lys Gln Asp Leu Asp
1105                1110                1115                1120
Gln Leu Arg Ser Ile Val Glu Lys Ser Glu Leu Trp Val Tyr Lys Gly
                1125                1130                1135
Gln Gly Pro Asp Glu Pro Met Asp Gly Ala Ser Gly Glu Asn Glu His
            1140                1145                1150
Lys Lys Thr Glu Glu Gly Thr Ser Lys Pro Leu Lys His Glu Ser Thr
        1155                1160                1165
Ser Ser Tyr Asn Tyr Arg Val Val Lys Glu Ile Leu Ile Arg Leu Ser
    1170                1175                1180
Lys Leu Cys Val Gln Glu Ser Ala Ser Val Arg Lys Ser Arg Lys Gln
1185                1190                1195                1200
Gln Gln Arg Leu Leu Arg Asn Met Gly Ala His Ala Val Val Leu Glu
                1205                1210                1215
Leu Leu Gln Ile Pro Tyr Glu Lys Ala Glu Asp Thr Lys Met Gln Glu
            1220                1225                1230
Ile Met Arg Leu Ala His Glu Phe Leu Gln Asn Phe Cys Ala Gly Asn
        1235                1240                1245
Gln Gln Asn Gln Ala Leu Leu His Lys His Ile Asn Leu Phe Leu Asn
    1250                1255                1260
Pro Gly Ile Leu Glu Ala Val Thr Met Gln His Ile Phe Met Asn Asn
1265                1270                1275                1280
Phe Gln Leu Cys Ser Glu Ile Asn Glu Arg Val Val Gln His Phe Val
                1285                1290                1295
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His Cys Ile Glu Thr His Gly Arg Asn Val Gln Tyr Ile Lys Phe Leu
1300 1305 1310
Gln Thr Ile Val Lys Ala Glu Gly Lys Phe Ile Lys Lys Cys Gln Asp
1315 1320 1325
Met Val Met Ala Glu Leu Val Asn Ser Gly Glu Asp Val Leu Val Phe
1330 1335 1340
Tyr Asn Asp Arg Ala Ser Phe Gln Thr Leu Ile Gln Met Met Arg Ser
1345 1350 1355 1360
Glu Arg Asp Arg Met Asp Glu Asn Ser Pro Leu Phe Met Tyr His Ile
1365 1370 1375
His Leu Val Glu Leu Leu Ala Val Cys Thr Glu Gly Lys Asn Val Tyr
1380 1385 1390
Thr Glu Ile Lys Cys Asn Ser Leu Leu Pro Leu Asp Asp Ile Val Arg
1395 1400 1405
Val Val Thr His Glu Asp Cys Ile Pro Glu Val Lys Ile Ala Tyr Ile
1410 1415 1420
Asn Phe Leu Asn His Cys Tyr Val Asp Thr Glu Val Glu Met Lys Glu
1425 1430 1435 1440
Ile Tyr Thr Ser Asn His Met Trp Lys Leu Phe Glu Asn Phe Leu Val
1445 1450 1455
Asp Ile Cys Arg Ala Cys Asn Asn Thr Ser Asp Arg Lys His Ala Asp
1460 1465 1470
Ser Val Leu Glu Lys Tyr Val Thr Glu Ile Val Met Ser Ile Val Thr
1475 1480 1485
Thr Phe Phe Ser Ser Pro Phe Ser Asp Gln Ser Thr Thr Leu Gln Thr
1490 1495 1500
Arg Gln Pro Val Phe Val Gln Leu Leu Gln Gly Val Phe Arg Val Tyr
1505 1510 1515 1520
His Cys Asn Trp Leu Met Pro Ser Gln Lys Ala Ser Val Glu Ser Cys
1525 1530 1535
Ile Arg Val Leu Ser Asp Val Ala Lys Ser Arg Ala Ile Ala Ile Pro
1540 1545 1550
Val Asp Leu Asp Ser Gln Val Asn Asn Leu Phe Leu Lys Ser His Asn
1555 1560 1565
Ile Val Gln Lys Thr Ala Met Asn Trp Arg Leu Ser Ala Arg Asn Ala
1570 1575 1580
Ala Arg Arg Asp Glu Val Leu Ala Ala Ser Arg Asp Tyr Arg Asn Ile
1585 1590 1595 1600
Ile Glu Arg Leu Gln Asp Ile Val Ser Ala Leu Glu Asp Arg Leu Arg
1605 1610 1615
Pro Leu Val Gln Ala Glu Leu Ser Val Leu Val Asp Val Leu His Arg
1620 1625 1630
Pro Glu Leu Leu Phe Pro Glu Asn Thr Asp Ala Arg Arg Lys Cys Glu
1635 1640 1645
Ser Gly Gly Phe Ile Cys Lys Leu Ile Lys His Thr Lys Gln Leu Leu
1650 1655 1660
Glu Glu Asn Glu Glu Lys Leu Cys Ile Lys Val Leu Gln Thr Leu Arg
1665 1670 1675 1680
Glu Met Met Thr Lys Asp Arg Gly Tyr Gly Glu Lys Gln Ile Ser Ile
1685 1690 1695
Asp Glu Leu Glu Asn Ala Glu Leu Pro Gln Pro Pro Glu Ala Glu Asn
1700 1705 1710
Ser Thr Glu Glu Leu Glu Pro Ser Pro Pro Leu Arg Gln Leu Glu Asp
1715 1720 1725
His Lys Arg Gly Glu Ala Leu Arg Gln Ile Leu Val Asn Arg Tyr Tyr
1730 1735 1740
Gly Asn Ile Arg Pro Ser Gly Arg Arg Glu Ser Leu Thr Ser Phe Gly
1745 1750 1755 1760
Asn Gly Pro Leu Ser Pro Gly Gly Pro Ser Lys Pro Gly Gly Gly Gly
1765 1770 1775

Gly Gly Pro Gly Ser Gly Ser Thr Ser Arg Gly Glu Met Ser Leu Ala
1780 1785 1790
Glu Val Gln Cys His Leu Asp Lys Glu Gly Ala Ser Asn Leu Val Ile
1795 1800 1805
Asp Leu Ile Met Asn Ala Ser Ser Asp Arg Val Phe His Glu Ser Ile
1810 1815 1820
Leu Leu Ala Ile Ala Leu Leu Glu Gly Gly Asn Thr Thr Ile Gln His
1825 1830 1835 1840
Ser Phe Phe Cys Arg Leu Thr Glu Asp Lys Lys Ser Glu Lys Phe Phe
1845 1850 1855
Lys Val Phe Tyr Asp Arg Met Lys Val Ala Gln Gln Glu Ile Lys Ala
1860 1865 1870
Thr Val Thr Val Asn Thr Ser Asp Leu Gly Asn Lys Lys Lys Asp Asp
1875 1880 1885
Glu Val Asp Arg Asp Ala Pro Ser Arg Lys Lys Ala Lys Glu Pro Thr
1890 1895 1900
Thr Gln Ile Thr Glu Glu Val Arg Asp Gln Leu Leu Glu Ala Ser Ala
1905 1910 1915 1920
Ala Thr Arg Lys Ala Phe Thr Thr Phe Arg Arg Glu Ala Asp Pro Asp
1925 1930 1935
Asp His Tyr Gln Ser Gly Glu Gly Thr Gln Ala Thr Thr Asp Lys Ala
1940 1945 1950
Lys Asp Asp Leu Glu Met Ser Ala Val Ile Thr Ile Met Gln Pro Ile
1955 1960 1965
Leu Arg Phe Leu Gln Leu Leu Cys Glu Asn His Asn Arg Asp Leu Gln
1970 1975 1980
Asn Phe Leu Arg Cys Gln Asn Asn Lys Thr Asn Tyr Asn Leu Val Cys
1985 1990 1995 2000
Glu Thr Leu Gln Phe Leu Asp Cys Ile Cys Gly Ser Thr Thr Gly Gly
2005 2010 2015
Leu Gly Leu Leu Gly Leu Tyr Ile Asn Glu Lys Asn Val Ala Leu Ile
2020 2025 2030
Asn Gln Thr Leu Glu Ser Leu Thr Glu Tyr Cys Gln Gly Pro Cys His
2035 2040 2045
Glu Asn Gln Asn Cys Ile Ala Thr His Glu Ser Asn Gly Ile Asp Ile
2050 2055 2060
Ile Thr Ala Leu Ile Leu Asn Asp Ile Asn Pro Leu Gly Lys Lys Arg
2065 2070 2075 2080
Met Asp Leu Val Leu Glu Leu Lys Asn Asn Ala Ser Lys Leu Leu Leu
2085 2090 2095
Ala Ile Met Glu Ser Arg His Asp Ser Glu Asn Ala Glu Arg Ile Leu
2100 2105 2110
Tyr Asn Met Arg Pro Lys Glu Leu Val Glu Val Ile Lys Lys Ala Tyr
2115 2120 2125
Met Gln Gly Glu Val Glu Phe Glu Asp Gly Glu Asn Gly Glu Asp Gly
2130 2135 2140
Ala Ala Ser Pro Arg Asn Val Gly His Asn Ile Tyr Ile Leu Ala His
2145 2150 2155 2160
Gln Leu Ala Arg His Asn Lys Glu Leu Gln Thr Met Leu Lys Pro Gly
2165 2170 2175
Gly Gln Val Asp Gly Asp Glu Ala Leu Glu Phe Tyr Ala Lys His Thr
2180 2185 2190
Ala Gln Ile Glu Ile Val Arg Leu Asp Arg Thr Met Glu Gln Ile Val
2195 2200 2205
Phe Pro Val Pro Ser Ile Cys Glu Phe Leu Thr Lys Glu Ser Lys Leu
2210 2215 2220
Arg Ile Tyr Tyr Thr Thr Glu Arg Asp Glu Gln Gly Ser Lys Ile Asn
2225 2230 2235 2240
Asp Phe Phe Leu Arg Ser Glu Asp Leu Phe Asn Glu Met Asn Trp Gln
2245 2250 2255

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Lys Lys Leu Arg Ala Gln Pro Val Leu Tyr Trp Cys Ala Arg Asn Met
            2260                2265                2270
Ser Phe Trp Ser Ser Ile Ser Phe Asn Leu Ala Val Leu Met Asn Leu
        2275                2280                2285
Leu Val Ala Phe Phe Tyr Pro Phe Lys Gly Val Arg Gly Gly Thr Leu
    2290                2295                2300
Glu Pro His Trp Ser Gly Leu Leu Trp Thr Ala Met Leu Ile Ser Leu
2305                2310                2315                2320
Ala Ile Val Ile Ala Leu Pro Lys Pro His Gly Ile Arg Ala Leu Ile
                2325                2330                2335
Ala Ser Thr Ile Leu Arg Leu Ile Phe Ser Val Gly Leu Gln Pro Thr
            2340                2345                2350
Leu Phe Leu Leu Gly Ala Phe Asn Val Cys Asn Lys Ile Ile Phe Leu
        2355                2360                2365
Met Ser Phe Val Gly Asn Cys Gly Thr Phe Thr Arg Gly Tyr Arg Ala
    2370                2375                2380
Met Val Leu Asp Val Glu Phe Leu Tyr His Leu Leu Tyr Leu Leu Ile
2385                2390                2395                2400
Cys Ala Met Gly Leu Phe Val His Glu Phe Phe Tyr Ser Leu Leu Leu
                2405                2410                2415
Phe Asp Leu Val Tyr Arg Glu Glu Thr Leu Leu Asn Val Ile Lys Ser
            2420                2425                2430
Val Thr Arg Asn Gly Arg Pro Ile Ile Leu Thr Ala Ala Leu Ala Leu
        2435                2440                2445
Ile Leu Val Tyr Leu Phe Ser Ile Val Gly Tyr Leu Phe Phe Lys Asp
    2450                2455                2460
Asp Phe Ile Leu Glu Val Asp Arg Leu Pro Asn Glu Thr Ala Gly Pro
2465                2470                2475                2480
Glu Thr Gly Glu Ser Leu Ala Asn Asp Phe Leu Tyr Ser Asp Val Cys
                2485                2490                2495
Arg Val Glu Thr Gly Glu Asn Cys Thr Ser Pro Ala Pro Lys Glu Glu.
            2500                2505                2510
Leu Leu Pro Val Glu Glu Thr Glu Gln Asp Lys Glu His Thr Cys Glu
        2515                2520                2525
Thr Leu Leu Met Cys Ile Val Thr Val Leu Ser His Gly Leu Arg Ser
    2530                2535                2540
Gly Gly Gly Val Gly Asp Val Leu Arg Lys Pro Ser Lys Glu Glu Pro
2545                2550                2555                2560
Leu Phe Ala Ala Arg Val Ile Tyr Asp Leu Leu Phe Phe Phe Met Val
                2565                2570                2575
Ile Ile Ile Val Leu Asn Leu Ile Phe Gly Val Ile Ile Asp Thr Phe
            2580                2585                2590
Ala Asp Leu Arg Ser Glu Lys Gln Lys Lys Glu Glu Ile Leu Lys Thr
        2595                2600                2605
Thr Cys Phe Ile Cys Gly Leu Glu Arg Asp Lys Phe Asp Asn Lys Thr
    2610                2615                2620
Val Thr Phe Glu Glu His Ile Lys Glu Glu His Asn Met Trp His Tyr
2625                2630                2635                2640
Leu Cys Phe Ile Val Leu Val Lys Val Lys Asp Ser Thr Glu Tyr Thr
                2645                2650                2655
Gly Pro Glu Ser Tyr Val Ala Glu Met Ile Arg Glu Arg Asn Leu Asp
            2660                2665                2670
Trp Phe Pro Arg Met Arg Ala Met Ser Leu Val Ser Ser Asp Ser Glu
        2675                2680                2685
Gly Glu Gln Asn Glu Leu Arg Asn Leu Gln Glu Lys Leu Glu Ser Thr
    2690                2695                2700
Met Lys Leu Val Thr Asn Leu Ser Gly Gln Leu Ser Glu Leu Lys Asp
2705                2710                2715                2720
Gln Met Thr Glu Gln Arg Lys Gln Lys Gln Arg Ile Gly Leu Leu Gly
                2725                2730                2735
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His Pro Pro His Met Asn Val Asn Pro Gln Gln Pro Ala
            2740                2745


<210> 3
<211> 2710
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/note =
      synthetic construct

<400> 3
Met Ser Asp Lys Met Ser Ser Phe Leu His Ile Gly Asp Ile Cys Ser
 1               5                  10                  15
Leu Tyr Ala Glu Gly Ser Thr Asn Gly Phe Ile Ser Thr Leu Gly Leu
            20                  25                  30
Val Asp Asp Arg Cys Val Val Gln Pro Glu Ala Gly Asp Leu Asn Asn
        35                  40                  45
Pro Pro Lys Lys Phe Arg Asp Cys Leu Phe Lys Leu Cys Pro Met Asn
    50                  55                  60
Arg Tyr Ser Ala Gln Lys Gln Phe Trp Lys Ala Ala Lys Pro Gly Ala
65                  70                  75                  80
Asn Ser Thr Thr Asp Ala Val Leu Leu Asn Lys Leu His His Ala Ala
                85                  90                  95
Asp Leu Glu Lys Lys Gln Asn Glu Thr Glu Asn Arg Lys Leu Leu Gly
            100                 105                 110
Thr Val Ile Gln Tyr Gly Asn Val Ile Gln Leu Leu His Leu Lys Ser
        115                 120                 125
Asn Lys Tyr Leu Thr Val Asn Lys Arg Leu Pro Ala Leu Leu Glu Lys
    130                 135                 140
Asn Ala Met Arg Val Thr Leu Asp Glu Ala Gly Asn Glu Gly Ser Trp
145                 150                 155                 160
Phe Tyr Ile Gln Pro Phe Tyr Lys Leu Arg Ser Ile Gly Asp Ser Val
                165                 170                 175
Val Ile Gly Asp Lys Val Val Leu Asn Pro Val Asn Ala Gly Gln Pro
            180                 185                 190
Leu His Ala Ser Ser His Gln Leu Val Asp Asn Pro Gly Cys Asn Glu
        195                 200                 205
Val Asn Ser Val Asn Cys Asn Thr Ser Trp Lys Ile Val Leu Phe Met
    210                 215                 220
Lys Trp Ser Asp Asn Lys Asp Asp Ile Leu Lys Gly Gly Asp Val Val
225                 230                 235                 240
Arg Leu Phe His Ala Glu Gln Glu Lys Phe Leu Thr Cys Asp Glu His
                245                 250                 255
Arg Lys Lys Gln His Val Phe Leu Arg Thr Thr Gly Arg Gln Ser Ala
            260                 265                 270
Thr Ser Ala Thr Ser Ser Lys Ala Leu Trp Glu Val Glu Val Val Gln
        275                 280                 285
His Asp Pro Cys Arg Gly Gly Ala Gly Tyr Trp Asn Ser Leu Phe Arg
    290                 295                 300
Phe Lys His Leu Ala Thr Gly His Tyr Leu Ala Ala Glu Val Asp Pro
305                 310                 315                 320
Asp Phe Glu Glu Glu Cys Leu Glu Phe Gln Pro Ser Val Asp Pro Asp
                325                 330                 335
Gln Asp Ala Ser Arg Ser Arg Leu Arg Asn Ala Gln Glu Lys Met Val
            340                 345                 350
Tyr Ser Leu Val Ser Val Pro Glu Gly Asn Asp Ile Ser Ser Ile Phe
        355                 360                 365
```

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Glu Leu Asp Pro Thr Thr Leu Arg Gly Gly Asp Ser Leu Val Pro Arg
    370                 375                 380
Asn Ser Tyr Val Arg Leu Arg His Leu Cys Thr Asn Thr Trp Val His
385                 390                 395                 400
Ser Thr Asn Ile Pro Ile Asp Lys Glu Glu Glu Lys Pro Val Met Leu
                405                 410                 415
Lys Ile Gly Thr Ser Pro Leu Lys Glu Asp Lys Glu Ala Phe Ala Ile
            420                 425                 430
Val Pro Val Ser Pro Ala Glu Val Arg Asp Leu Asp Phe Ala Asn Asp
        435                 440                 445
Ala Ser Lys Val Leu Gly Ser Ile Ala Gly Lys Leu Glu Lys Gly Thr
    450                 455                 460
Ile Thr Gln Asn Glu Arg Arg Ser Val Thr Lys Leu Leu Glu Asp Leu
465                 470                 475                 480
Val Tyr Phe Val Thr Gly Gly Thr Asn Ser Gly Gln Asp Val Leu Glu
                485                 490                 495
Val Val Phe Ser Lys Pro Asn Arg Glu Arg Gln Lys Leu Met Arg Glu
            500                 505                 510
Gln Asn Ile Leu Lys Gln Ile Phe Lys Leu Leu Gln Ala Pro Phe Thr
        515                 520                 525
Asp Cys Gly Asp Gly Pro Met Leu Arg Leu Glu Glu Leu Gly Asp Gln
    530                 535                 540
Arg His Ala Pro Phe Arg His Ile Cys Arg Leu Cys Tyr Arg Val Leu
545                 550                 555                 560
Arg His Ser Gln Gln Asp Tyr Arg Lys Asn Gln Glu Tyr Ile Ala Lys
                565                 570                 575
Gln Phe Gly Phe Met Gln Lys Gln Ile Gly Tyr Asp Val Leu Ala Glu
            580                 585                 590
Asp Thr Ile Thr Ala Leu Leu His Asn Asn Arg Lys Leu Leu Glu Lys
        595                 600                 605
His Ile Thr Ala Ala Glu Ile Asp Thr Phe Val Ser Leu Val Arg Lys
    610                 615                 620
Asn Arg Glu Pro Arg Phe Leu Asp Tyr Leu Ser Asp Leu Cys Val Ser
625                 630                 635                 640
Met Asn Lys Ser Ile Pro Val Thr Gln Glu Leu Ile Cys Lys Ala Val
                645                 650                 655
Leu Asn Pro Thr Asn Ala Asp Ile Leu Ile Glu Thr Lys Leu Val Leu
            660                 665                 670
Ser Arg Phe Glu Phe Glu Gly Val Ser Thr Gly Glu Asn Ala Leu Glu
        675                 680                 685
Ala Gly Glu Asp Glu Glu Glu Val Trp Leu Phe Trp Arg Asp Ser Asn
    690                 695                 700
Lys Glu Ile Arg Ser Lys Ser Val Arg Glu Leu Ala Gln Asp Ala Lys
705                 710                 715                 720
Glu Gly Gln Lys Glu Asp Arg Asp Val Leu Ser Tyr Tyr Arg Tyr Gln
                725                 730                 735
Leu Asn Leu Phe Ala Arg Met Cys Leu Asp Arg Gln Tyr Leu Ala Ile
            740                 745                 750
Asn Glu Ile Ser Gly Gln Leu Asp Val Asp Leu Ile Leu Arg Cys Met
        755                 760                 765
Ser Asp Glu Asn Leu Pro Tyr Asp Leu Arg Ala Ser Phe Cys Arg Leu
    770                 775                 780
Met Leu His Met His Val Asp Arg Asp Pro Gln Glu Gln Val Thr Pro
785                 790                 795                 800
Val Lys Tyr Ala Arg Leu Trp Ser Glu Ile Pro Ser Glu Ile Ala Ile
                805                 810                 815
Asp Asp Tyr Asp Ser Ser Gly Ala Ser Lys Asp Glu Ile Lys Glu Arg
            820                 825                 830
Phe Ala Gln Thr Met Glu Phe Val Glu Glu Tyr Leu Arg Asp Val Val
        835                 840                 845
```

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Cys Gln Arg Phe Pro Phe Ser Asp Lys Glu Lys Asn Lys Leu Thr Phe
    850                 855                 860
Glu Val Val Asn Leu Ala Arg Asn Leu Ile Tyr Phe Gly Phe Tyr Asn
865                 870                 875                 880
Phe Ser Asp Leu Leu Arg Leu Thr Lys Ile Leu Leu Ala Ile Leu Asp
                885                 890                 895
Cys Val His Val Thr Thr Ile Phe Pro Ile Ser Lys Met Thr Lys Gly
            900                 905                 910
Glu Glu Asn Lys Gly Ser Asn Val Met Arg Ser Ile His Gly Val Gly
        915                 920                 925
Glu Leu Met Thr Gln Val Val Leu Arg Gly Gly Gly Phe Leu Pro Met
    930                 935                 940
Thr Pro Met Ala Ala Ala Pro Glu Gly Asn Val Lys Gln Ala Glu Pro
945                 950                 955                 960
Glu Lys Glu Asp Ile Met Val Met Asp Thr Lys Leu Lys Ile Ile Glu
                965                 970                 975
Ile Leu Gln Phe Ile Leu Asn Val Arg Leu Asp Tyr Arg Ile Ser Cys
            980                 985                 990
Leu Leu Cys Ile Phe Lys Arg Glu Phe Asp Glu Ser Asn Ser Gln Ser
        995                 1000                1005
Ser Glu Thr Ser Ser Gly Asn Ser Ser Gln Glu Gly Pro Ser Asn Val
    1010                1015                1020
Pro Gly Ala Leu Asp Phe Glu His Ile Glu Glu Gln Ala Glu Gly Ile
1025                1030                1035                1040
Phe Gly Gly Ser Glu Glu Asn Thr Pro Leu Asp Leu Asp Asp His Gly
                1045                1050                1055
Gly Arg Thr Phe Leu Arg Val Leu Leu His Leu Thr Met His Asp Tyr
            1060                1065                1070
Pro Pro Leu Val Ser Gly Ala Leu Gln Leu Leu Phe Arg His Phe Ser
        1075                1080                1085
Gln Arg Gln Glu Val Leu Gln Ala Phe Lys Gln Val Gln Leu Leu Val
    1090                1095                1100
Thr Ser Gln Asp Val Asp Asn Tyr Lys Gln Ile Lys Gln Asp Leu Asp
1105                1110                1115                1120
Gln Leu Arg Ser Ile Val Glu Lys Ser Glu Leu Trp Val Tyr Lys Gly
                1125                1130                1135
Gln Gly Pro Asp Glu Pro Met Asp Gly Ala Ser Gly Glu Asn Glu His
            1140                1145                1150
Lys Lys Thr Glu Glu Gly Thr Ser Lys Pro Leu Lys His Glu Ser Thr
        1155                1160                1165
Ser Ser Tyr Asn Tyr Arg Val Val Lys Glu Ile Leu Ile Arg Leu Ser
    1170                1175                1180
Lys Leu Cys Val Gln Glu Ser Ala Ser Val Arg Lys Ser Arg Lys Gln
1185                1190                1195                1200
Gln Gln Arg Leu Leu Arg Asn Met Gly Ala His Ala Val Val Leu Glu
                1205                1210                1215
Leu Leu Gln Ile Pro Tyr Glu Lys Ala Glu Asp Thr Lys Met Gln Glu
            1220                1225                1230
Ile Met Arg Leu Ala His Glu Phe Leu Gln Asn Phe Cys Ala Gly Asn
        1235                1240                1245
Gln Gln Asn Gln Ala Leu Leu His Lys His Ile Asn Leu Phe Leu Asn
    1250                1255                1260
Pro Gly Ile Leu Glu Ala Val Thr Met Gln His Ile Phe Met Asn Asn
1265                1270                1275                1280
Phe Gln Leu Cys Ser Glu Ile Asn Glu Arg Val Val Gln His Phe Val
                1285                1290                1295
His Cys Ile Glu Thr His Gly Arg Asn Val Gln Tyr Ile Lys Phe Leu
            1300                1305                1310
Gln Thr Ile Val Lys Ala Glu Gly Lys Phe Ile Lys Lys Cys Gln Asp
        1315                1320                1325
```

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Met Val Met Ala Glu Leu Val Asn Ser Gly Glu Asp Val Leu Val Phe
    1330                1335                1340
Tyr Asn Asp Arg Ala Ser Phe Gln Thr Leu Ile Gln Met Met Arg Ser
1345                1350                1355                1360
Glu Arg Asp Arg Met Asp Glu Asn Ser Pro Leu Phe Met Tyr His Ile
                1365                1370                1375
His Leu Val Glu Leu Leu Ala Val Cys Thr Glu Gly Lys Asn Val Tyr
            1380                1385                1390
Thr Glu Ile Lys Cys Asn Ser Leu Leu Pro Leu Asp Asp Ile Val Arg
        1395                1400                1405
Val Val Thr His Glu Asp Cys Ile Pro Glu Val Lys Ile Ala Tyr Ile
    1410                1415                1420
Asn Phe Leu Asn His Cys Tyr Val Asp Thr Glu Val Glu Met Lys Glu
1425                1430                1435                1440
Ile Tyr Thr Ser Asn His Met Trp Lys Leu Phe Glu Asn Phe Leu Val
                1445                1450                1455
Asp Ile Cys Arg Ala Cys Asn Asn Thr Ser Asp Arg Lys His Ala Asp
            1460                1465                1470
Ser Val Leu Glu Lys Tyr Val Thr Glu Ile Val Met Ser Ile Val Thr
        1475                1480                1485
Thr Phe Phe Ser Ser Pro Phe Ser Asp Gln Ser Thr Thr Leu Gln Thr
    1490                1495                1500
Arg Gln Pro Val Phe Val Gln Leu Leu Gln Gly Val Phe Arg Val Tyr
1505                1510                1515                1520
His Cys Asn Trp Leu Met Pro Ser Gln Lys Ala Ser Val Glu Ser Cys
                1525                1530                1535
Ile Arg Val Leu Ser Asp Val Ala Lys Ser Arg Ala Ile Ala Ile Pro
            1540                1545                1550
Val Asp Leu Asp Ser Gln Val Asn Asn Leu Phe Leu Lys Ser His Asn
        1555                1560                1565
Ile Val Gln Lys Thr Ala Met Asn Trp Arg Leu Ser Ala Arg Asn Ala
    1570                1575                1580
Ala Arg Arg Asp Asp Val Leu Ala Ala Ser Arg Asp Tyr Arg Asn Ile
1585                1590                1595                1600
Ile Glu Arg Leu Gln Asp Ile Val Ser Ala Leu Glu Asp Arg Leu Arg
                1605                1610                1615
Pro Leu Val Gln Ala Glu Leu Ser Val Leu Val Asp Val Leu His Arg
            1620                1625                1630
Pro Glu Leu Leu Phe Pro Glu Asn Thr Asp Ala Arg Arg Lys Cys Glu
        1635                1640                1645
Ser Gly Gly Phe Ile Cys Lys Leu Ile Lys His Thr Lys Gln Leu Leu
    1650                1655                1660
Glu Glu Asn Glu Glu Lys Leu Cys Ile Lys Val Leu Gln Thr Leu Arg
1665                1670                1675                1680
Glu Met Met Thr Lys Asp Arg Gly Tyr Gly Glu Lys Gly Glu Ala Leu
                1685                1690                1695
Arg Gln Ile Leu Val Asn Arg Tyr Tyr Gly Asn Ile Arg Pro Ser Gly
            1700                1705                1710
Arg Arg Glu Ser Leu Thr Ser Phe Gly Asn Gly Pro Leu Ser Pro Gly
        1715                1720                1725
Gly Pro Ser Lys Pro Gly Gly Gly Gly Gly Gly Pro Gly Ser Gly Ser
    1730                1735                1740
Thr Ser Arg Gly Glu Met Ser Leu Ala Glu Val Gln Cys His Leu Asp
1745                1750                1755                1760
Lys Glu Gly Ala Ser Asn Leu Val Ile Asp Leu Ile Met Asn Ala Ser
                1765                1770                1775
Ser Asp Arg Val Phe His Glu Ser Ile Leu Leu Ala Ile Ala Leu Leu
            1780                1785                1790
Glu Gly Gly Asn Thr Thr Ile Gln His Ser Phe Phe Cys Arg Leu Thr
        1795                1800                1805
```

Glu Asp Lys Lys Ser Glu Lys Phe Phe Lys Val Phe Tyr Asp Arg Met
1810 1815 1820
Lys Val Ala Gln Gln Glu Ile Lys Ala Thr Val Thr Val Asn Thr Ser
1825 1830 1835 1840
Asp Leu Gly Asn Lys Lys Lys Asp Asp Glu Val Asp Arg Asp Ala Pro
1845 1850 1855
Ser Arg Lys Lys Ala Lys Glu Pro Thr Thr Gln Ile Thr Glu Glu Val
1860 1865 1870
Arg Asp Gln Leu Leu Glu Ala Ser Ala Ala Thr Arg Lys Ala Phe Thr
1875 1880 1885
Thr Phe Arg Arg Glu Ala Asp Pro Asp Asp His Tyr Gln Ser Gly Glu
1890 1895 1900
Gly Thr Gln Ala Thr Thr Asp Lys Ala Lys Asp Asp Leu Glu Met Ser
1905 1910 1915 1920
Ala Val Ile Thr Ile Met Gln Pro Ile Leu Arg Phe Leu Gln Leu Leu
1925 1930 1935
Cys Glu Asn His Asn Arg Asp Leu Gln Asn Phe Leu Arg Cys Gln Asn
1940 1945 1950
Asn Lys Thr Asn Tyr Asn Leu Val Cys Glu Thr Leu Gln Phe Leu Asp
1955 1960 1965
Cys Ile Cys Gly Ser Thr Thr Gly Gly Leu Gly Leu Leu Gly Leu Tyr
1970 1975 1980
Ile Asn Glu Lys Asn Val Ala Leu Ile Asn Gln Thr Leu Glu Ser Leu
1985 1990 1995 2000
Thr Glu Tyr Cys Gln Gly Pro Cys His Glu Asn Gln Asn Cys Ile Ala
2005 2010 2015
Thr His Glu Ser Asn Gly Ile Asp Ile Ile Thr Ala Leu Ile Leu Asn
2020 2025 2030
Asp Ile Asn Pro Leu Gly Lys Lys Arg Met Asp Leu Val Leu Glu Leu
2035 2040 2045
Lys Asn Asn Ala Ser Lys Leu Leu Leu Ala Ile Met Glu Ser Arg His
2050 2055 2060
Asp Ser Glu Asn Ala Glu Arg Ile Leu Tyr Asn Met Arg Pro Lys Glu
2065 2070 2075 2080
Leu Val Glu Val Ile Lys Lys Ala Tyr Met Gln Gly Glu Val Glu Phe
2085 2090 2095
Glu Asp Gly Glu Asn Gly Glu Asp Gly Ala Ala Ser Pro Arg Asn Val
2100 2105 2110
Gly His Asn Ile Tyr Ile Leu Ala His Gln Leu Ala Arg His Asn Lys
2115 2120 2125
Glu Leu Gln Thr Met Leu Lys Pro Gly Gly Gln Val Asp Gly Asp Glu
2130 2135 2140
Ala Leu Glu Phe Tyr Ala Lys His Thr Ala Gln Ile Glu Ile Val Arg
2145 2150 2155 2160
Leu Asp Arg Thr Met Glu Gln Ile Val Phe Pro Val Pro Ser Ile Cys
2165 2170 2175
Glu Phe Leu Thr Lys Glu Ser Lys Leu Arg Ile Tyr Tyr Thr Thr Glu
2180 2185 2190
Arg Asp Glu Gln Gly Ser Lys Ile Asn Asp Phe Phe Leu Arg Ser Glu
2195 2200 2205
Asp Leu Phe Asn Glu Met Asn Trp Gln Lys Lys Leu Arg Ala Gln Pro
2210 2215 2220
Val Leu Tyr Trp Cys Ala Arg Asn Met Ser Phe Trp Ser Ser Ile Ser
2225 2230 2235 2240
Phe Asn Leu Ala Val Leu Met Asn Leu Leu Val Ala Phe Phe Tyr Pro
2245 2250 2255
Phe Lys Gly Val Arg Gly Gly Thr Leu Glu Pro His Trp Ser Gly Leu
2260 2265 2270
Leu Trp Thr Ala Met Leu Ile Ser Leu Ala Ile Val Ile Ala Leu Pro
2275 2280 2285

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Lys Pro His Gly Ile Arg Ala Leu Ile Ala Ser Thr Ile Leu Arg Leu
    2290                2295                2300
Ile Phe Ser Val Gly Leu Gln Pro Thr Leu Phe Leu Leu Gly Ala Phe
2305                2310                2315                2320
Asn Val Cys Asn Lys Ile Ile Phe Leu Met Ser Phe Val Gly Asn Cys
                2325                2330                2335
Gly Thr Phe Thr Arg Gly Tyr Arg Ala Met Val Leu Asp Val Glu Phe
            2340                2345                2350
Leu Tyr His Leu Leu Tyr Leu Leu Ile Cys Ala Met Gly Leu Phe Val
        2355                2360                2365
His Glu Phe Phe Tyr Ser Leu Leu Leu Phe Asp Leu Val Tyr Arg Glu
    2370                2375                2380
Glu Thr Leu Leu Asn Val Ile Lys Ser Val Thr Arg Asn Gly Arg Pro
2385                2390                2395                2400
Ile Ile Leu Thr Ala Ala Leu Ala Leu Ile Leu Val Tyr Leu Phe Ser
                2405                2410                2415
Ile Val Gly Tyr Leu Phe Phe Lys Asp Asp Phe Ile Leu Glu Val Asp
            2420                2425                2430
Arg Leu Pro Asn Glu Thr Ala Gly Pro Glu Thr Gly Glu Ser Leu Ala
        2435                2440                2445
Asn Asp Phe Leu Tyr Ser Asp Val Cys Arg Val Glu Thr Gly Glu Asn
    2450                2455                2460
Cys Thr Ser Pro Ala Pro Lys Glu Glu Leu Leu Pro Val Glu Glu Thr
2465                2470                2475                2480
Glu Gln Asp Lys Glu His Thr Cys Glu Thr Leu Leu Met Cys Ile Val
                2485                2490                2495
Thr Val Leu Ser His Gly Leu Arg Ser Gly Gly Gly Val Gly Asp Val
            2500                2505                2510
Leu Arg Lys Pro Ser Lys Glu Glu Pro Leu Phe Ala Ala Arg Val Ile
        2515                2520                2525
Tyr Asp Leu Leu Phe Phe Phe Met Val Ile Ile Ile Val Leu Asn Leu
    2530                2535                2540
Ile Phe Gly Val Ile Ile Asp Thr Phe Ala Asp Leu Arg Ser Glu Lys
2545                2550                2555                2560
Gln Lys Lys Glu Glu Ile Leu Lys Thr Thr Cys Phe Ile Cys Gly Leu
                2565                2570                2575
Glu Arg Asp Lys Phe Asp Asn Lys Thr Val Thr Phe Glu Glu His Ile
            2580                2585                2590
Lys Glu Glu His Asn Met Trp His Tyr Leu Cys Phe Ile Val Leu Val
        2595                2600                2605
Lys Val Lys Asp Ser Thr Glu Tyr Thr Gly Pro Glu Ser Tyr Val Ala
    2610                2615                2620
Glu Met Ile Arg Glu Arg Asn Leu Asp Trp Phe Pro Arg Met Arg Ala
2625                2630                2635                2640
Met Ser Leu Val Ser Ser Asp Ser Glu Gly Glu Gln Asn Glu Leu Arg
                2645                2650                2655
Asn Leu Gln Glu Lys Leu Glu Ser Thr Met Lys Leu Val Thr Asn Leu
            2660                2665                2670
Ser Gly Gln Leu Ser Glu Leu Lys Asp Gln Met Thr Glu Gln Arg Lys
        2675                2680                2685
Gln Lys Gln Arg Ile Gly Leu Leu Gly His Pro Pro His Met Asn Val
    2690                2695                2700
Asn Pro Gln Gln Pro Ala
2705                2710
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<210> 4
<211> 2749
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/note =
synthetic construct

<400> 4

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Met Ser Asp Lys Met Ser Ser Phe Leu His Ile Gly Asp Ile Cys Ser
 1               5                  10                  15
Leu Tyr Ala Glu Gly Ser Thr Asn Gly Phe Ile Ser Thr Leu Gly Leu
            20                  25                  30
Val Asp Asp Arg Cys Val Val Gln Pro Glu Ala Gly Asp Leu Asn Asn
        35                  40                  45
Pro Pro Lys Lys Phe Arg Asp Cys Leu Phe Lys Leu Cys Pro Met Asn
    50                  55                  60
Arg Tyr Ser Ala Gln Lys Gln Phe Trp Lys Ala Ala Lys Pro Gly Ala
65                  70                  75                  80
Asn Ser Thr Thr Asp Ala Val Leu Leu Asn Lys Leu His His Ala Ala
                85                  90                  95
Asp Leu Glu Lys Lys Gln Asn Glu Thr Glu Asn Arg Lys Leu Leu Gly
            100                 105                 110
Thr Val Ile Gln Tyr Gly Asn Val Ile Gln Leu Leu His Leu Lys Ser
        115                 120                 125
Asn Lys Tyr Leu Thr Val Asn Lys Arg Leu Pro Ala Leu Leu Glu Lys
    130                 135                 140
Asn Ala Met Arg Val Thr Leu Asp Glu Ala Gly Asn Glu Gly Ser Trp
145                 150                 155                 160
Phe Tyr Ile Gln Pro Phe Tyr Lys Leu Arg Ser Ile Gly Asp Ser Val
                165                 170                 175
Val Ile Gly Asp Lys Val Val Leu Asn Pro Val Asn Ala Gly Gln Pro
            180                 185                 190
Leu His Ala Ser Ser His Gln Leu Val Asp Asn Pro Gly Cys Asn Glu
        195                 200                 205
Val Asn Ser Val Asn Cys Asn Thr Ser Trp Lys Ile Val Leu Phe Met
    210                 215                 220
Lys Trp Ser Asp Asn Lys Asp Asp Ile Leu Lys Gly Gly Asp Val Val
225                 230                 235                 240
Arg Leu Phe His Ala Glu Gln Glu Lys Phe Leu Thr Cys Asp Glu His
                245                 250                 255
Arg Lys Lys Gln His Val Phe Leu Arg Thr Thr Gly Arg Gln Ser Ala
            260                 265                 270
Thr Ser Ala Thr Ser Ser Lys Ala Leu Trp Glu Val Glu Val Val Gln
        275                 280                 285
His Asp Pro Cys Arg Gly Gly Ala Gly Tyr Trp Asn Ser Leu Phe Arg
    290                 295                 300
Phe Lys His Leu Ala Thr Gly His Tyr Leu Ala Ala Glu Val Asp Pro
305                 310                 315                 320
Asp Phe Glu Glu Glu Cys Leu Glu Phe Gln Pro Ser Val Asp Pro Asp
                325                 330                 335
Gln Asp Ala Ser Arg Ser Arg Leu Arg Asn Ala Gln Glu Lys Met Val
            340                 345                 350
Tyr Ser Leu Val Ser Val Pro Glu Gly Asn Asp Ile Ser Ser Ile Phe
        355                 360                 365
Glu Leu Asp Pro Thr Thr Leu Arg Gly Gly Asp Ser Leu Val Pro Arg
    370                 375                 380
Asn Ser Tyr Val Arg Leu Arg His Leu Cys Thr Asn Thr Trp Val His
385                 390                 395                 400
Ser Thr Asn Ile Pro Ile Asp Lys Glu Glu Glu Lys Pro Val Met Leu
                405                 410                 415
Lys Ile Gly Thr Ser Pro Leu Lys Glu Asp Lys Glu Ala Phe Ala Ile
            420                 425                 430
Val Pro Val Ser Pro Ala Glu Val Arg Asp Leu Asp Phe Ala Asn Asp
        435                 440                 445
```

```
Ala Ser Lys Val Leu Gly Ser Ile Ala Gly Lys Leu Glu Lys Gly Thr
    450                 455                 460
Ile Thr Gln Asn Glu Arg Arg Ser Val Thr Lys Leu Leu Glu Asp Leu
465                 470                 475                 480
Val Tyr Phe Val Thr Gly Gly Thr Asn Ser Gly Gln Asp Val Leu Glu
                485                 490                 495
Val Val Phe Ser Lys Pro Asn Arg Glu Arg Gln Lys Leu Met Arg Glu
            500                 505                 510
Gln Asn Ile Leu Lys Gln Ile Phe Lys Leu Leu Gln Ala Pro Phe Thr
        515                 520                 525
Asp Cys Gly Asp Gly Pro Met Leu Arg Leu Glu Glu Leu Gly Asp Gln
    530                 535                 540
Arg His Ala Pro Phe Arg His Ile Cys Arg Leu Cys Tyr Arg Val Leu
545                 550                 555                 560
Arg His Ser Gln Gln Asp Tyr Arg Lys Asn Gln Glu Tyr Ile Ala Lys
                565                 570                 575
Gln Phe Gly Phe Met Gln Lys Gln Ile Gly Tyr Asp Val Leu Ala Glu
            580                 585                 590
Asp Thr Ile Thr Ala Leu Leu His Asn Asn Arg Lys Leu Leu Glu Lys
        595                 600                 605
His Ile Thr Ala Ala Glu Ile Asp Thr Phe Val Ser Leu Val Arg Lys
    610                 615                 620
Asn Arg Glu Pro Arg Phe Leu Asp Tyr Leu Ser Asp Leu Cys Val Ser
625                 630                 635                 640
Met Asn Lys Ser Ile Pro Val Thr Gln Glu Leu Ile Cys Lys Ala Val
                645                 650                 655
Leu Asn Pro Thr Asn Ala Asp Ile Leu Ile Glu Thr Lys Leu Val Leu
            660                 665                 670
Ser Arg Phe Glu Phe Glu Gly Val Ser Thr Gly Glu Asn Ala Leu Glu
        675                 680                 685
Ala Gly Glu Asp Glu Glu Glu Val Trp Leu Phe Trp Arg Asp Ser Asn
    690                 695                 700
Lys Glu Ile Arg Ser Lys Ser Val Arg Glu Leu Ala Gln Asp Ala Lys
705                 710                 715                 720
Glu Gly Gln Lys Glu Asp Arg Asp Val Leu Ser Tyr Tyr Arg Tyr Gln
                725                 730                 735
Leu Asn Leu Phe Ala Arg Met Cys Leu Asp Arg Gln Tyr Leu Ala Ile
            740                 745                 750
Asn Glu Ile Ser Gly Gln Leu Asp Val Asp Leu Ile Leu Arg Cys Met
        755                 760                 765
Ser Asp Glu Asn Leu Pro Tyr Asp Leu Arg Ala Ser Phe Cys Arg Leu
    770                 775                 780
Met Leu His Met His Val Asp Arg Asp Pro Gln Glu Gln Val Thr Pro
785                 790                 795                 800
Val Lys Tyr Ala Arg Leu Trp Ser Glu Ile Pro Ser Glu Ile Ala Ile
                805                 810                 815
Asp Asp Tyr Asp Ser Ser Gly Ala Ser Lys Asp Glu Ile Lys Glu Arg
            820                 825                 830
Phe Ala Gln Thr Met Glu Phe Val Glu Glu Tyr Leu Arg Asp Val Val
        835                 840                 845
Cys Gln Arg Phe Pro Phe Ser Asp Lys Glu Lys Asn Lys Leu Thr Phe
    850                 855                 860
Glu Val Val Asn Leu Ala Arg Asn Leu Ile Tyr Phe Gly Phe Tyr Asn
865                 870                 875                 880
Phe Ser Asp Leu Leu Arg Leu Thr Lys Ile Leu Leu Ala Ile Leu Asp
                885                 890                 895
Cys Val His Val Thr Thr Ile Phe Pro Ile Ser Lys Met Thr Lys Gly
            900                 905                 910
Glu Glu Asn Lys Gly Ser Asn Val Met Arg Ser Ile His Gly Val Gly
        915                 920                 925
```

```
Glu Leu Met Thr Gln Val Val Leu Arg Gly Gly Gly Phe Leu Pro Met
    930                 935                 940
Thr Pro Met Ala Ala Ala Pro Glu Gly Asn Val Lys Gln Ala Glu Pro
945                 950                 955                 960
Glu Lys Glu Asp Ile Met Val Met Asp Thr Lys Leu Lys Ile Ile Glu
                965                 970                 975
Ile Leu Gln Phe Ile Leu Asn Val Arg Leu Asp Tyr Arg Ile Ser Cys
            980                 985                 990
Leu Leu Cys Ile Phe Lys Arg Glu Phe Asp Glu Ser Asn Ser Gln Ser
        995                 1000                1005
Ser Glu Thr Ser Ser Gly Asn Ser Ser Gln Glu Gly Pro Ser Asn Val
    1010                1015                1020
Pro Gly Ala Leu Asp Phe Glu His Ile Glu Glu Gln Ala Glu Gly Ile
1025                1030                1035                1040
Phe Gly Gly Ser Glu Glu Asn Thr Pro Leu Asp Leu Asp Asp His Gly
                1045                1050                1055
Gly Arg Thr Phe Leu Arg Val Leu Leu His Leu Thr Met His Asp Tyr
            1060                1065                1070
Pro Pro Leu Val Ser Gly Ala Leu Gln Leu Leu Phe Arg His Phe Ser
        1075                1080                1085
Gln Arg Gln Glu Val Leu Gln Ala Phe Lys Gln Val Gln Leu Leu Val
    1090                1095                1100
Thr Ser Gln Asp Val Asp Asn Tyr Lys Gln Ile Lys Gln Asp Leu Asp
1105                1110                1115                1120
Gln Leu Arg Ser Ile Val Glu Lys Ser Glu Leu Trp Val Tyr Lys Gly
                1125                1130                1135
Gln Gly Pro Asp Glu Pro Met Asp Gly Ala Ser Gly Glu Asn Glu His
            1140                1145                1150
Lys Lys Thr Glu Glu Gly Thr Ser Lys Pro Leu Lys His Glu Ser Thr
        1155                1160                1165
Ser Ser Tyr Asn Tyr Arg Val Val Lys Glu Ile Leu Ile Arg Leu Ser
    1170                1175                1180
Lys Leu Cys Val Gln Glu Ser Ala Ser Val Arg Lys Ser Arg Lys Gln
1185                1190                1195                1200
Gln Gln Arg Leu Leu Arg Asn Met Gly Ala His Ala Val Val Leu Glu
                1205                1210                1215
Leu Leu Gln Ile Pro Tyr Glu Lys Ala Glu Asp Thr Lys Met Gln Glu
            1220                1225                1230
Ile Met Arg Leu Ala His Glu Phe Leu Gln Asn Phe Cys Ala Gly Asn
        1235                1240                1245
Gln Gln Asn Gln Ala Leu Leu His Lys His Ile Asn Leu Phe Leu Asn
    1250                1255                1260
Pro Gly Ile Leu Glu Ala Val Thr Met Gln His Ile Phe Met Asn Asn
1265                1270                1275                1280
Phe Gln Leu Cys Ser Glu Ile Asn Glu Arg Val Val Gln His Phe Val
                1285                1290                1295
His Cys Ile Glu Thr His Gly Arg Asn Val Gln Tyr Ile Lys Phe Leu
            1300                1305                1310
Gln Thr Ile Val Lys Ala Glu Gly Lys Phe Ile Lys Lys Cys Gln Asp
        1315                1320                1325
Met Val Met Ala Glu Leu Val Asn Ser Gly Glu Asp Val Leu Val Phe
    1330                1335                1340
Tyr Asn Asp Arg Ala Ser Phe Gln Thr Leu Ile Gln Met Met Arg Ser
1345                1350                1355                1360
Glu Arg Asp Arg Met Asp Glu Asn Ser Pro Leu Phe Met Tyr His Ile
                1365                1370                1375
His Leu Val Glu Leu Leu Ala Val Cys Thr Glu Gly Lys Asn Val Tyr
            1380                1385                1390
Thr Glu Ile Lys Cys Asn Ser Leu Leu Pro Leu Asp Asp Ile Val Arg
        1395                1400                1405
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Val Val Thr His Glu Asp Cys Ile Pro Glu Val Lys Ile Ala Tyr Ile
    1410                1415                1420
Asn Phe Leu Asn His Cys Tyr Val Asp Thr Glu Val Glu Met Lys Glu
1425                1430                1435                1440
Ile Tyr Thr Ser Asn His Met Trp Lys Leu Phe Glu Asn Phe Leu Val
                1445                1450                1455
Asp Ile Cys Arg Ala Cys Asn Asn Thr Ser Asp Arg Lys His Ala Asp
            1460                1465                1470
Ser Val Leu Glu Lys Tyr Val Thr Glu Ile Val Met Ser Ile Val Thr
        1475                1480                1485
Thr Phe Phe Ser Ser Pro Phe Ser Asp Gln Ser Thr Thr Leu Gln Thr
    1490                1495                1500
Arg Gln Pro Val Phe Val Gln Leu Leu Gln Gly Val Phe Arg Val Tyr
1505                1510                1515                1520
His Cys Asn Trp Leu Met Pro Ser Gln Lys Ala Ser Val Glu Ser Cys
                1525                1530                1535
Ile Arg Val Leu Ser Asp Val Ala Lys Ser Arg Ala Ile Ala Ile Pro
            1540                1545                1550
Val Asp Leu Asp Ser Gln Val Asn Asn Leu Phe Leu Lys Ser His Asn
        1555                1560                1565
Ile Val Gln Lys Thr Ala Met Asn Trp Arg Leu Ser Ala Arg Asn Ala
    1570                1575                1580
Ala Arg Arg Asp Asp Val Leu Ala Ala Ser Arg Asp Tyr Arg Asn Ile
1585                1590                1595                1600
Ile Glu Arg Leu Gln Asp Ile Val Ser Ala Leu Glu Asp Arg Leu Arg
                1605                1610                1615
Pro Leu Val Gln Ala Glu Leu Ser Val Leu Val Asp Val Leu His Arg
            1620                1625                1630
Pro Glu Leu Leu Phe Pro Glu Asn Thr Asp Ala Arg Arg Lys Cys Glu
        1635                1640                1645
Ser Gly Gly Phe Ile Cys Lys Leu Ile Lys His Thr Lys Gln Leu Leu
    1650                1655                1660
Glu Glu Asn Glu Glu Lys Leu Cys Ile Lys Val Leu Gln Thr Leu Arg
1665                1670                1675                1680
Glu Met Met Thr Lys Asp Arg Gly Tyr Gly Glu Lys Gln Ile Ser Ile
                1685                1690                1695
Asp Glu Leu Glu Asn Ala Glu Leu Pro Gln Pro Pro Glu Ala Glu Asn
            1700                1705                1710
Ser Thr Glu Glu Leu Glu Pro Ser Pro Pro Leu Arg Gln Leu Glu Asp
        1715                1720                1725
His Lys Arg Gly Glu Ala Leu Arg Gln Ile Leu Val Asn Arg Tyr Tyr
    1730                1735                1740
Gly Asn Ile Arg Pro Ser Gly Arg Arg Glu Ser Leu Thr Ser Phe Gly
1745                1750                1755                1760
Asn Gly Pro Leu Ser Pro Gly Gly Pro Ser Lys Pro Gly Gly Gly Gly
                1765                1770                1775
Gly Gly Pro Gly Ser Gly Ser Thr Ser Arg Gly Glu Met Ser Leu Ala
            1780                1785                1790
Glu Val Gln Cys His Leu Asp Lys Glu Gly Ala Ser Asn Leu Val Ile
        1795                1800                1805
Asp Leu Ile Met Asn Ala Ser Ser Asp Arg Val Phe His Glu Ser Ile
    1810                1815                1820
Leu Leu Ala Ile Ala Leu Leu Glu Gly Gly Asn Thr Thr Ile Gln His
1825                1830                1835                1840
Ser Phe Phe Cys Arg Leu Thr Glu Asp Lys Lys Ser Glu Lys Phe Phe
                1845                1850                1855
Lys Val Phe Tyr Asp Arg Met Lys Val Ala Gln Gln Glu Ile Lys Ala
            1860                1865                1870
Thr Val Thr Val Asn Thr Ser Asp Leu Gly Asn Lys Lys Lys Asp Asp
        1875                1880                1885
```

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Glu Val Asp Arg Asp Ala Pro Ser Arg Lys Lys Ala Lys Glu Pro Thr
    1890                1895                1900
Thr Gln Ile Thr Glu Glu Val Arg Asp Gln Leu Leu Glu Ala Ser Ala
1905                1910                1915                1920
Ala Thr Arg Lys Ala Phe Thr Thr Phe Arg Arg Glu Ala Asp Pro Asp
                1925                1930                1935
Asp His Tyr Gln Ser Gly Glu Gly Thr Gln Ala Thr Thr Asp Lys Ala
            1940                1945                1950
Lys Asp Asp Leu Glu Met Ser Ala Val Ile Thr Ile Met Gln Pro Ile
        1955                1960                1965
Leu Arg Phe Leu Gln Leu Leu Cys Glu Asn His Asn Arg Asp Leu Gln
    1970                1975                1980
Asn Phe Leu Arg Cys Gln Asn Asn Lys Thr Asn Tyr Asn Leu Val Cys
1985                1990                1995                2000
Glu Thr Leu Gln Phe Leu Asp Cys Ile Cys Gly Ser Thr Thr Gly Gly
                2005                2010                2015
Leu Gly Leu Leu Gly Leu Tyr Ile Asn Glu Lys Asn Val Ala Leu Ile
            2020                2025                2030
Asn Gln Thr Leu Glu Ser Leu Thr Glu Tyr Cys Gln Gly Pro Cys His
        2035                2040                2045
Glu Asn Gln Asn Cys Ile Ala Thr His Glu Ser Asn Gly Ile Asp Ile
    2050                2055                2060
Ile Thr Ala Leu Ile Leu Asn Asp Ile Asn Pro Leu Gly Lys Lys Arg
2065                2070                2075                2080
Met Asp Leu Val Leu Glu Leu Lys Asn Asn Ala Ser Lys Leu Leu Leu
                2085                2090                2095
Ala Ile Met Glu Ser Arg His Asp Ser Glu Asn Ala Glu Arg Ile Leu
            2100                2105                2110
Tyr Asn Met Arg Pro Lys Glu Leu Val Glu Val Ile Lys Lys Ala Tyr
        2115                2120                2125
Met Gln Gly Glu Val Glu Phe Glu Asp Gly Glu Asn Gly Glu Asp Gly
    2130                2135                2140
Ala Ala Ser Pro Arg Asn Val Gly His Asn Ile Tyr Ile Leu Ala His
2145                2150                2155                2160
Gln Leu Ala Arg His Asn Lys Glu Leu Gln Thr Met Leu Lys Pro Gly
                2165                2170                2175
Gly Gln Val Asp Gly Asp Glu Ala Leu Glu Phe Tyr Ala Lys His Thr
            2180                2185                2190
Ala Gln Ile Glu Ile Val Arg Leu Asp Arg Thr Met Glu Gln Ile Val
        2195                2200                2205
Phe Pro Val Pro Ser Ile Cys Glu Phe Leu Thr Lys Glu Ser Lys Leu
    2210                2215                2220
Arg Ile Tyr Tyr Thr Thr Glu Arg Asp Glu Gln Gly Ser Lys Ile Asn
2225                2230                2235                2240
Asp Phe Phe Leu Arg Ser Glu Asp Leu Phe Asn Glu Met Asn Trp Gln
                2245                2250                2255
Lys Lys Leu Arg Ala Gln Pro Val Leu Tyr Trp Cys Ala Arg Asn Met
            2260                2265                2270
Ser Phe Trp Ser Ser Ile Ser Phe Asn Leu Ala Val Leu Met Asn Leu
        2275                2280                2285
Leu Val Ala Phe Phe Tyr Pro Phe Lys Gly Val Arg Gly Gly Thr Leu
    2290                2295                2300
Glu Pro His Trp Ser Gly Leu Leu Trp Thr Ala Met Leu Ile Ser Leu
2305                2310                2315                2320
Ala Ile Val Ile Ala Leu Pro Lys Pro His Gly Ile Arg Ala Leu Ile
                2325                2330                2335
Ala Ser Thr Ile Leu Arg Leu Ile Phe Ser Val Gly Leu Gln Pro Thr
            2340                2345                2350
Leu Phe Leu Leu Gly Ala Phe Asn Val Cys Asn Lys Ile Ile Phe Leu
        2355                2360                2365
```

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Met Ser Phe Val Gly Asn Cys Gly Thr Phe Thr Arg Gly Tyr Arg Ala
    2370                2375                2380
Met Val Leu Asp Val Glu Phe Leu Tyr His Leu Leu Tyr Leu Leu Ile
2385                2390                2395                2400
Cys Ala Met Gly Leu Phe Val His Glu Phe Phe Tyr Ser Leu Leu Leu
                2405                2410                2415
Phe Asp Leu Val Tyr Arg Glu Glu Thr Leu Leu Asn Val Ile Lys Ser
            2420                2425                2430
Val Thr Arg Asn Gly Arg Pro Ile Ile Leu Thr Ala Ala Leu Ala Leu
        2435                2440                2445
Ile Leu Val Tyr Leu Phe Ser Ile Val Gly Tyr Leu Phe Phe Lys Asp
    2450                2455                2460
Asp Phe Ile Leu Glu Val Asp Arg Leu Pro Asn Glu Thr Ala Gly Pro
2465                2470                2475                2480
Glu Thr Gly Glu Ser Leu Ala Asn Asp Phe Leu Tyr Ser Asp Val Cys
                2485                2490                2495
Arg Val Glu Thr Gly Glu Asn Cys Thr Ser Pro Ala Pro Lys Glu Glu
            2500                2505                2510
Leu Leu Pro Val Glu Glu Thr Glu Gln Asp Lys Glu His Thr Cys Glu
        2515                2520                2525
Thr Leu Leu Met Cys Ile Val Thr Val Leu Ser His Gly Leu Arg Ser
    2530                2535                2540
Gly Gly Gly Val Gly Asp Val Leu Arg Lys Pro Ser Lys Glu Glu Pro
2545                2550                2555                2560
Leu Phe Ala Ala Arg Val Ile Tyr Asp Leu Leu Phe Phe Phe Met Val
                2565                2570                2575
Ile Ile Ile Val Leu Asn Leu Ile Phe Gly Val Ile Ile Asp Thr Phe
            2580                2585                2590
Ala Asp Leu Arg Ser Glu Lys Gln Lys Lys Glu Glu Ile Leu Lys Thr
        2595                2600                2605
Thr Cys Phe Ile Cys Gly Leu Glu Arg Asp Lys Phe Asp Asn Lys Thr
    2610                2615                2620
Val Thr Phe Glu Glu His Ile Lys Glu Glu His Asn Met Trp His Tyr
2625                2630                2635                2640
Leu Cys Phe Ile Val Leu Val Lys Val Lys Asp Ser Thr Glu Tyr Thr
                2645                2650                2655
Gly Pro Glu Ser Tyr Val Ala Glu Met Ile Arg Glu Arg Asn Leu Asp
            2660                2665                2670
Trp Phe Pro Arg Met Arg Ala Met Ser Leu Val Ser Ser Asp Ser Glu
        2675                2680                2685
Gly Glu Gln Asn Glu Leu Arg Asn Leu Gln Glu Lys Leu Glu Ser Thr
    2690                2695                2700
Met Lys Leu Val Thr Asn Leu Ser Gly Gln Leu Ser Glu Leu Lys Asp
2705                2710                2715                2720
Gln Met Thr Glu Gln Arg Lys Gln Lys Gln Arg Ile Gly Leu Leu Gly
                2725                2730                2735
His Pro Pro His Met Asn Val Asn Pro Gln Gln Pro Ala
            2740                2745


<210> 5
<211> 2710
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/note =
      synthetic construct

<400> 5
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Met Ser Asp Lys Met Ser Ser Phe Leu His Ile Gly Asp Ile Cys Ser
 1               5                  10                  15
Leu Tyr Ala Glu Gly Ser Thr Asn Gly Phe Ile Ser Thr Leu Gly Leu
            20                  25                  30
Val Asp Asp Arg Cys Val Val Gln Pro Glu Ala Gly Asp Leu Asn Asn
        35                  40                  45
Pro Pro Lys Lys Phe Arg Asp Cys Leu Phe Lys Leu Cys Pro Met Asn
    50                  55                  60
Arg Tyr Ser Ala Gln Lys Gln Phe Trp Lys Ala Ala Lys Pro Gly Ala
65                  70                  75                  80
Asn Ser Thr Thr Asp Ala Val Leu Leu Asn Lys Leu His His Ala Ala
                85                  90                  95
Asp Leu Glu Lys Lys Gln Asn Glu Thr Glu Asn Arg Lys Leu Leu Gly
            100                 105                 110
Thr Val Ile Gln Tyr Gly Asn Val Ile Gln Leu Leu His Leu Lys Ser
        115                 120                 125
Asn Lys Tyr Leu Thr Val Asn Lys Arg Leu Pro Ala Leu Leu Glu Lys
    130                 135                 140
Asn Ala Met Arg Val Thr Leu Asp Glu Ala Gly Asn Glu Gly Ser Trp
145                 150                 155                 160
Phe Tyr Ile Gln Pro Phe Tyr Lys Leu Arg Ser Ile Gly Asp Ser Val
                165                 170                 175
Val Ile Gly Asp Lys Val Val Leu Asn Pro Val Asn Ala Gly Gln Pro
            180                 185                 190
Leu His Ala Ser Ser His Gln Leu Val Asp Asn Pro Gly Cys Asn Glu
        195                 200                 205
Val Asn Ser Val Asn Cys Asn Thr Ser Trp Lys Ile Val Leu Phe Met
    210                 215                 220
Lys Trp Ser Asp Asn Lys Asp Asp Ile Leu Lys Gly Gly Asp Val Val
225                 230                 235                 240
Arg Leu Phe His Ala Glu Gln Glu Lys Phe Leu Thr Cys Asp Glu His
                245                 250                 255
Arg Lys Lys Gln His Val Phe Leu Arg Thr Thr Gly Arg Gln Ser Ala
            260                 265                 270
Thr Ser Ala Thr Ser Ser Lys Ala Leu Trp Glu Val Glu Val Val Gln
        275                 280                 285
His Asp Pro Cys Arg Gly Gly Ala Gly Tyr Trp Asn Ser Leu Phe Arg
    290                 295                 300
Phe Lys His Leu Ala Thr Gly His Tyr Leu Ala Ala Glu Val Asp Pro
305                 310                 315                 320
Asp Phe Glu Glu Glu Cys Leu Glu Phe Gln Pro Ser Val Asp Pro Asp
                325                 330                 335
Gln Asp Ala Ser Arg Ser Arg Leu Arg Asn Ala Gln Glu Lys Met Val
            340                 345                 350
Tyr Ser Leu Val Ser Val Pro Glu Gly Asn Asp Ile Ser Ser Ile Phe
        355                 360                 365
Glu Leu Asp Pro Thr Thr Leu Arg Gly Gly Asp Ser Leu Val Pro Arg
    370                 375                 380
Asn Ser Tyr Val Arg Leu Arg His Leu Cys Thr Asn Thr Trp Val His
385                 390                 395                 400
Ser Thr Asn Ile Pro Ile Asp Lys Glu Glu Glu Lys Pro Val Met Leu
                405                 410                 415
Lys Ile Gly Thr Ser Pro Leu Lys Glu Asp Lys Glu Ala Phe Ala Ile
            420                 425                 430
Val Pro Val Ser Pro Ala Glu Val Arg Asp Leu Asp Phe Ala Asn Asp
        435                 440                 445
Ala Ser Lys Val Leu Gly Ser Ile Ala Gly Lys Leu Glu Lys Gly Thr
    450                 455                 460
Ile Thr Gln Asn Glu Arg Arg Ser Val Thr Lys Leu Leu Glu Asp Leu
465                 470                 475                 480
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Val Tyr Phe Val Thr Gly Gly Thr Asn Ser Gly Gln Asp Val Leu Glu
                485                 490                 495
Val Val Phe Ser Lys Pro Asn Arg Glu Arg Gln Lys Leu Met Arg Glu
            500                 505                 510
Gln Asn Ile Leu Lys Gln Ile Phe Lys Leu Leu Gln Ala Pro Phe Thr
        515                 520                 525
Asp Cys Gly Asp Gly Pro Met Leu Arg Leu Glu Glu Leu Gly Asp Gln
    530                 535                 540
Arg His Ala Pro Phe Arg His Ile Cys Arg Leu Cys Tyr Arg Val Leu
545                 550                 555                 560
Arg His Ser Gln Gln Asp Tyr Arg Lys Asn Gln Glu Tyr Ile Ala Lys
                565                 570                 575
Gln Phe Gly Phe Met Gln Lys Gln Ile Gly Tyr Asp Val Leu Ala Glu
            580                 585                 590
Asp Thr Ile Thr Ala Leu Leu His Asn Asn Arg Lys Leu Leu Glu Lys
        595                 600                 605
His Ile Thr Ala Ala Glu Ile Asp Thr Phe Val Ser Leu Val Arg Lys
    610                 615                 620
Asn Arg Glu Pro Arg Phe Leu Asp Tyr Leu Ser Asp Leu Cys Val Ser
625                 630                 635                 640
Met Asn Lys Ser Ile Pro Val Thr Gln Glu Leu Ile Cys Lys Ala Val
                645                 650                 655
Leu Asn Pro Thr Asn Ala Asp Ile Leu Ile Glu Thr Lys Leu Val Leu
            660                 665                 670
Ser Arg Phe Glu Phe Glu Gly Val Ser Thr Gly Glu Asn Ala Leu Glu
        675                 680                 685
Ala Gly Glu Asp Glu Glu Glu Val Trp Leu Phe Trp Arg Asp Ser Asn
    690                 695                 700
Lys Glu Ile Arg Ser Lys Ser Val Arg Glu Leu Ala Gln Asp Ala Lys
705                 710                 715                 720
Glu Gly Gln Lys Glu Asp Arg Asp Val Leu Ser Tyr Tyr Arg Tyr Gln
                725                 730                 735
Leu Asn Leu Phe Ala Arg Met Cys Leu Asp Arg Gln Tyr Leu Ala Ile
            740                 745                 750
Asn Glu Ile Ser Gly Gln Leu Asp Val Asp Leu Ile Leu Arg Cys Met
        755                 760                 765
Ser Asp Glu Asn Leu Pro Tyr Asp Leu Arg Ala Ser Phe Cys Arg Leu
    770                 775                 780
Met Leu His Met His Val Asp Arg Asp Pro Gln Glu Gln Val Thr Pro
785                 790                 795                 800
Val Lys Tyr Ala Arg Leu Trp Ser Glu Ile Pro Ser Glu Ile Ala Ile
                805                 810                 815
Asp Asp Tyr Asp Ser Ser Gly Ala Ser Lys Asp Glu Ile Lys Glu Arg
            820                 825                 830
Phe Ala Gln Thr Met Glu Phe Val Glu Glu Tyr Leu Arg Asp Val Val
        835                 840                 845
Cys Gln Arg Phe Pro Phe Ser Asp Lys Glu Lys Asn Lys Leu Thr Phe
    850                 855                 860
Glu Val Val Asn Leu Ala Arg Asn Leu Ile Tyr Phe Gly Phe Tyr Asn
865                 870                 875                 880
Phe Ser Asp Leu Leu Arg Leu Thr Lys Ile Leu Leu Ala Ile Leu Asp
                885                 890                 895
Cys Val His Val Thr Thr Ile Phe Pro Ile Ser Lys Met Thr Lys Gly
            900                 905                 910
Glu Glu Asn Lys Gly Ser Asn Val Met Arg Ser Ile His Gly Val Gly
        915                 920                 925
Glu Leu Met Thr Gln Val Val Leu Arg Gly Gly Gly Phe Leu Pro Met
    930                 935                 940
Thr Pro Met Ala Ala Ala Pro Glu Gly Asn Val Lys Gln Ala Glu Pro
945                 950                 955                 960
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Glu Lys Glu Asp Ile Met Val Met Asp Thr Lys Leu Lys Ile Ile Glu
                965                 970                 975
Ile Leu Gln Phe Ile Leu Asn Val Arg Leu Asp Tyr Arg Ile Ser Cys
            980                 985                 990
Leu Leu Cys Ile Phe Lys Arg Glu Phe Asp Glu Ser Asn Ser Gln Ser
        995                 1000                1005
Ser Glu Thr Ser Ser Gly Asn Ser Ser Gln Glu Gly Pro Ser Asn Val
    1010                1015                1020
Pro Gly Ala Leu Asp Phe Glu His Ile Glu Glu Gln Ala Glu Gly Ile
1025                1030                1035                1040
Phe Gly Gly Ser Glu Glu Asn Thr Pro Leu Asp Leu Asp Asp His Gly
                1045                1050                1055
Gly Arg Thr Phe Leu Arg Val Leu Leu His Leu Thr Met His Asp Tyr
            1060                1065                1070
Pro Pro Leu Val Ser Gly Ala Leu Gln Leu Leu Phe Arg His Phe Ser
        1075                1080                1085
Gln Arg Gln Glu Val Leu Gln Ala Phe Lys Gln Val Gln Leu Leu Val
    1090                1095                1100
Thr Ser Gln Asp Val Asp Asn Tyr Lys Gln Ile Lys Gln Asp Leu Asp
1105                1110                1115                1120
Gln Leu Arg Ser Ile Val Glu Lys Ser Glu Leu Trp Val Tyr Lys Gly
                1125                1130                1135
Gln Gly Pro Asp Glu Pro Met Asp Gly Ala Ser Gly Glu Asn Glu His
            1140                1145                1150
Lys Lys Thr Glu Glu Gly Thr Ser Lys Pro Leu Lys His Glu Ser Thr
        1155                1160                1165
Ser Ser Tyr Asn Tyr Arg Val Val Lys Glu Ile Leu Ile Arg Leu Ser
    1170                1175                1180
Lys Leu Cys Val Gln Glu Ser Ala Ser Val Arg Lys Ser Arg Lys Gln
1185                1190                1195                1200
Gln Gln Arg Leu Leu Arg Asn Met Gly Ala His Ala Val Val Leu Glu
                1205                1210                1215
Leu Leu Gln Ile Pro Tyr Glu Lys Ala Glu Asp Thr Lys Met Gln Glu
            1220                1225                1230
Ile Met Arg Leu Ala His Glu Phe Leu Gln Asn Phe Cys Ala Gly Asn
        1235                1240                1245
Gln Gln Asn Gln Ala Leu Leu His Lys His Ile Asn Leu Phe Leu Asn
    1250                1255                1260
Pro Gly Ile Leu Glu Ala Val Thr Met Gln His Ile Phe Met Asn Asn
1265                1270                1275                1280
Phe Gln Leu Cys Ser Glu Ile Asn Glu Arg Val Val Gln His Phe Val
                1285                1290                1295
His Cys Ile Glu Thr His Gly Arg Asn Val Gln Tyr Ile Lys Phe Leu
            1300                1305                1310
Gln Thr Ile Val Lys Ala Glu Gly Lys Phe Ile Lys Lys Cys Gln Asp
        1315                1320                1325
Met Val Met Ala Glu Leu Val Asn Ser Gly Glu Asp Val Leu Val Phe
    1330                1335                1340
Tyr Asn Asp Arg Ala Ser Phe Gln Thr Leu Ile Gln Met Met Arg Ser
1345                1350                1355                1360
Glu Arg Asp Arg Met Asp Glu Asn Ser Pro Leu Phe Met Tyr His Ile
                1365                1370                1375
His Leu Val Glu Leu Leu Ala Val Cys Thr Glu Gly Lys Asn Val Tyr
            1380                1385                1390
Thr Glu Ile Lys Cys Asn Ser Leu Leu Pro Leu Asp Asp Ile Val Arg
        1395                1400                1405
Val Val Thr His Glu Asp Cys Ile Pro Glu Val Lys Ile Ala Tyr Ile
    1410                1415                1420
Asn Phe Leu Asn His Cys Tyr Val Asp Thr Glu Val Glu Met Lys Glu
1425                1430                1435                1440
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Ile Tyr Thr Ser Asn His Met Trp Lys Leu Phe Glu Asn Phe Leu Val
                1445                1450                1455
Asp Ile Cys Arg Ala Cys Asn Asn Thr Ser Asp Arg Lys His Ala Asp
            1460                1465                1470
Ser Val Leu Glu Lys Tyr Val Thr Glu Ile Val Met Ser Ile Val Thr
        1475                1480                1485
Thr Phe Phe Ser Ser Pro Phe Ser Asp Gln Ser Thr Thr Leu Gln Thr
    1490                1495                1500
Arg Gln Pro Val Phe Val Gln Leu Leu Gln Gly Val Phe Arg Val Tyr
1505                1510                1515                1520
His Cys Asn Trp Leu Met Pro Ser Gln Lys Ala Ser Val Glu Ser Cys
                1525                1530                1535
Ile Arg Val Leu Ser Asp Val Ala Lys Ser Arg Ala Ile Ala Ile Pro
            1540                1545                1550
Val Asp Leu Asp Ser Gln Val Asn Asn Leu Phe Leu Lys Ser His Asn
        1555                1560                1565
Ile Val Gln Lys Thr Ala Met Asn Trp Arg Leu Ser Ala Arg Asn Ala
    1570                1575                1580
Ala Arg Arg Asp Ser Val Leu Ala Ala Ser Arg Asp Tyr Arg Asn Ile
1585                1590                1595                1600
Ile Glu Arg Leu Gln Asp Ile Val Ser Ala Leu Glu Asp Arg Leu Arg
                1605                1610                1615
Pro Leu Val Gln Ala Glu Leu Ser Val Leu Val Asp Val Leu His Arg
            1620                1625                1630
Pro Glu Leu Leu Phe Pro Glu Asn Thr Asp Ala Arg Arg Lys Cys Glu
        1635                1640                1645
Ser Gly Gly Phe Ile Cys Lys Leu Ile Lys His Thr Lys Gln Leu Leu
    1650                1655                1660
Glu Glu Asn Glu Glu Lys Leu Cys Ile Lys Val Leu Gln Thr Leu Arg
1665                1670                1675                1680
Glu Met Met Thr Lys Asp Arg Gly Tyr Gly Glu Lys Gly Glu Ala Leu
                1685                1690                1695
Arg Gln Ile Leu Val Asn Arg Tyr Tyr Gly Asn Ile Arg Pro Ser Gly
            1700                1705                1710
Arg Arg Glu Glu Leu Thr Ser Phe Gly Asn Gly Pro Leu Ser Pro Gly
        1715                1720                1725
Gly Pro Ser Lys Pro Gly Gly Gly Gly Gly Gly Pro Gly Ser Gly Ser
    1730                1735                1740
Thr Ser Arg Gly Glu Met Ser Leu Ala Glu Val Gln Cys His Leu Asp
1745                1750                1755                1760
Lys Glu Gly Ala Ser Asn Leu Val Ile Asp Leu Ile Met Asn Ala Ser
                1765                1770                1775
Ser Asp Arg Val Phe His Glu Ser Ile Leu Leu Ala Ile Ala Leu Leu
            1780                1785                1790
Glu Gly Gly Asn Thr Thr Ile Gln His Ser Phe Phe Cys Arg Leu Thr
        1795                1800                1805
Glu Asp Lys Lys Ser Glu Lys Phe Phe Lys Val Phe Tyr Asp Arg Met
    1810                1815                1820
Lys Val Ala Gln Gln Glu Ile Lys Ala Thr Val Thr Val Asn Thr Ser
1825                1830                1835                1840
Asp Leu Gly Asn Lys Lys Lys Asp Asp Glu Val Asp Arg Asp Ala Pro
                1845                1850                1855
Ser Arg Lys Lys Ala Lys Glu Pro Thr Thr Gln Ile Thr Glu Glu Val
            1860                1865                1870
Arg Asp Gln Leu Leu Glu Ala Ser Ala Ala Thr Arg Lys Ala Phe Thr
        1875                1880                1885
Thr Phe Arg Arg Glu Ala Asp Pro Asp Asp His Tyr Gln Ser Gly Glu
    1890                1895                1900
Gly Thr Gln Ala Thr Thr Asp Lys Ala Lys Asp Asp Leu Glu Met Ser
1905                1910                1915                1920
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Ala Val Ile Thr Ile Met Gln Pro Ile Leu Arg Phe Leu Gln Leu Leu
                1925                1930                1935
Cys Glu Asn His Asn Arg Asp Leu Gln Asn Phe Leu Arg Cys Gln Asn
            1940                1945                1950
Asn Lys Thr Asn Tyr Asn Leu Val Cys Glu Thr Leu Gln Phe Leu Asp
        1955                1960                1965
Cys Ile Cys Gly Ser Thr Thr Gly Gly Leu Gly Leu Leu Gly Leu Tyr
    1970                1975                1980
Ile Asn Glu Lys Asn Val Ala Leu Ile Asn Gln Thr Leu Glu Ser Leu
1985                1990                1995                2000
Thr Glu Tyr Cys Gln Gly Pro Cys His Glu Asn Gln Asn Cys Ile Ala
                2005                2010                2015
Thr His Glu Ser Asn Gly Ile Asp Ile Ile Thr Ala Leu Ile Leu Asn
            2020                2025                2030
Asp Ile Asn Pro Leu Gly Lys Lys Arg Met Asp Leu Val Leu Glu Leu
        2035                2040                2045
Lys Asn Asn Ala Ser Lys Leu Leu Leu Ala Ile Met Glu Ser Arg His
    2050                2055                2060
Asp Ser Glu Asn Ala Glu Arg Ile Leu Tyr Asn Met Arg Pro Lys Glu
2065                2070                2075                2080
Leu Val Glu Val Ile Lys Lys Ala Tyr Met Gln Gly Glu Val Glu Phe
                2085                2090                2095
Glu Asp Gly Glu Asn Gly Glu Asp Gly Ala Ala Ser Pro Arg Asn Val
            2100                2105                2110
Gly His Asn Ile Tyr Ile Leu Ala His Gln Leu Ala Arg His Asn Lys
        2115                2120                2125
Glu Leu Gln Thr Met Leu Lys Pro Gly Gly Gln Val Asp Gly Asp Glu
    2130                2135                2140
Ala Leu Glu Phe Tyr Ala Lys His Thr Ala Gln Ile Glu Ile Val Arg
2145                2150                2155                2160
Leu Asp Arg Thr Met Glu Gln Ile Val Phe Pro Val Pro Ser Ile Cys
                2165                2170                2175
Glu Phe Leu Thr Lys Glu Ser Lys Leu Arg Ile Tyr Tyr Thr Thr Glu
            2180                2185                2190
Arg Asp Glu Gln Gly Ser Lys Ile Asn Asp Phe Phe Leu Arg Ser Glu
        2195                2200                2205
Asp Leu Phe Asn Glu Met Asn Trp Gln Lys Lys Leu Arg Ala Gln Pro
    2210                2215                2220
Val Leu Tyr Trp Cys Ala Arg Asn Met Ser Phe Trp Ser Ser Ile Ser
2225                2230                2235                2240
Phe Asn Leu Ala Val Leu Met Asn Leu Leu Val Ala Phe Phe Tyr Pro
                2245                2250                2255
Phe Lys Gly Val Arg Gly Gly Thr Leu Glu Pro His Trp Ser Gly Leu
            2260                2265                2270
Leu Trp Thr Ala Met Leu Ile Ser Leu Ala Ile Val Ile Ala Leu Pro
        2275                2280                2285
Lys Pro His Gly Ile Arg Ala Leu Ile Ala Ser Thr Ile Leu Arg Leu
    2290                2295                2300
Ile Phe Ser Val Gly Leu Gln Pro Thr Leu Phe Leu Leu Gly Ala Phe
2305                2310                2315                2320
Asn Val Cys Asn Lys Ile Ile Phe Leu Met Ser Phe Val Gly Asn Cys
                2325                2330                2335
Gly Thr Phe Thr Arg Gly Tyr Arg Ala Met Val Leu Asp Val Glu Phe
            2340                2345                2350
Leu Tyr His Leu Leu Tyr Leu Leu Ile Cys Ala Met Gly Leu Phe Val
        2355                2360                2365
His Glu Phe Phe Tyr Ser Leu Leu Leu Phe Asp Leu Val Tyr Arg Glu
    2370                2375                2380
Glu Thr Leu Leu Asn Val Ile Lys Ser Val Thr Arg Asn Gly Arg Pro
2385                2390                2395                2400
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Ile Ile Leu Thr Ala Ala Leu Ala Leu Ile Leu Val Tyr Leu Phe Ser
                2405                2410                2415
Ile Val Gly Tyr Leu Phe Phe Lys Asp Asp Phe Ile Leu Glu Val Asp
            2420                2425                2430
Arg Leu Pro Asn Glu Thr Ala Gly Pro Glu Thr Gly Glu Ser Leu Ala
        2435                2440                2445
Asn Asp Phe Leu Tyr Ser Asp Val Cys Arg Val Glu Thr Gly Glu Asn
    2450                2455                2460
Cys Thr Ser Pro Ala Pro Lys Glu Glu Leu Leu Pro Val Glu Glu Thr
2465                2470                2475                2480
Glu Gln Asp Lys Glu His Thr Cys Glu Thr Leu Leu Met Cys Ile Val
                2485                2490                2495
Thr Val Leu Ser His Gly Leu Arg Ser Gly Gly Gly Val Gly Asp Val
            2500                2505                2510
Leu Arg Lys Pro Ser Lys Glu Glu Pro Leu Phe Ala Ala Arg Val Ile
        2515                2520                2525
Tyr Asp Leu Leu Phe Phe Phe Met Val Ile Ile Ile Val Leu Asn Leu
    2530                2535                2540
Ile Phe Gly Val Ile Ile Asp Thr Phe Ala Asp Leu Arg Ser Glu Lys
2545                2550                2555                2560
Gln Lys Lys Glu Glu Ile Leu Lys Thr Thr Cys Phe Ile Cys Gly Leu
                2565                2570                2575
Glu Arg Asp Lys Phe Asp Asn Lys Thr Val Thr Phe Glu Glu His Ile
            2580                2585                2590
Lys Glu Glu His Asn Met Trp His Tyr Leu Cys Phe Ile Val Leu Val
        2595                2600                2605
Lys Val Lys Asp Ser Thr Glu Tyr Thr Gly Pro Glu Ser Tyr Val Ala
    2610                2615                2620
Glu Met Ile Arg Glu Arg Asn Leu Asp Trp Phe Pro Arg Met Arg Ala
2625                2630                2635                2640
Met Ser Leu Val Ser Ser Asp Ser Glu Gly Glu Gln Asn Glu Leu Arg
                2645                2650                2655
Asn Leu Gln Glu Lys Leu Glu Ser Thr Met Lys Leu Val Thr Asn Leu
            2660                2665                2670
Ser Gly Gln Leu Ser Glu Leu Lys Asp Gln Met Thr Glu Gln Arg Lys
        2675                2680                2685
Gln Lys Gln Arg Ile Gly Leu Leu Gly His Pro Pro His Met Asn Val
    2690                2695                2700
Asn Pro Gln Gln Pro Ala
2705                2710


<210> 6
<211> 2749
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/note =
      synthetic construct

<400> 6
Met Ser Asp Lys Met Ser Ser Phe Leu His Ile Gly Asp Ile Cys Ser
 1               5                  10                  15
Leu Tyr Ala Glu Gly Ser Thr Asn Gly Phe Ile Ser Thr Leu Gly Leu
            20                  25                  30
Val Asp Asp Arg Cys Val Val Gln Pro Glu Ala Gly Asp Leu Asn Asn
        35                  40                  45
Pro Pro Lys Lys Phe Arg Asp Cys Leu Phe Lys Leu Cys Pro Met Asn
    50                  55                  60
```

```
Arg Tyr Ser Ala Gln Lys Gln Phe Trp Lys Ala Ala Lys Pro Gly Ala
65                  70                  75                  80
Asn Ser Thr Thr Asp Ala Val Leu Leu Asn Lys Leu His His Ala Ala
                85                  90                  95
Asp Leu Glu Lys Lys Gln Asn Glu Thr Glu Asn Arg Lys Leu Leu Gly
            100                 105                 110
Thr Val Ile Gln Tyr Gly Asn Val Ile Gln Leu Leu His Leu Lys Ser
        115                 120                 125
Asn Lys Tyr Leu Thr Val Asn Lys Arg Leu Pro Ala Leu Leu Glu Lys
    130                 135                 140
Asn Ala Met Arg Val Thr Leu Asp Glu Ala Gly Asn Glu Gly Ser Trp
145                 150                 155                 160
Phe Tyr Ile Gln Pro Phe Tyr Lys Leu Arg Ser Ile Gly Asp Ser Val
                165                 170                 175
Val Ile Gly Asp Lys Val Val Leu Asn Pro Val Asn Ala Gly Gln Pro
            180                 185                 190
Leu His Ala Ser Ser His Gln Leu Val Asp Asn Pro Gly Cys Asn Glu
        195                 200                 205
Val Asn Ser Val Asn Cys Asn Thr Ser Trp Lys Ile Val Leu Phe Met
    210                 215                 220
Lys Trp Ser Asp Asn Lys Asp Asp Ile Leu Lys Gly Gly Asp Val Val
225                 230                 235                 240
Arg Leu Phe His Ala Glu Gln Glu Lys Phe Leu Thr Cys Asp Glu His
                245                 250                 255
Arg Lys Lys Gln His Val Phe Leu Arg Thr Thr Gly Arg Gln Ser Ala
            260                 265                 270
Thr Ser Ala Thr Ser Ser Lys Ala Leu Trp Glu Val Glu Val Val Gln
        275                 280                 285
His Asp Pro Cys Arg Gly Gly Ala Gly Tyr Trp Asn Ser Leu Phe Arg
    290                 295                 300
Phe Lys His Leu Ala Thr Gly His Tyr Leu Ala Ala Glu Val Asp Pro
305                 310                 315                 320
Asp Phe Glu Glu Glu Cys Leu Glu Phe Gln Pro Ser Val Asp Pro Asp
                325                 330                 335
Gln Asp Ala Ser Arg Ser Arg Leu Arg Asn Ala Gln Glu Lys Met Val
            340                 345                 350
Tyr Ser Leu Val Ser Val Pro Glu Gly Asn Asp Ile Ser Ser Ile Phe
        355                 360                 365
Glu Leu Asp Pro Thr Thr Leu Arg Gly Gly Asp Ser Leu Val Pro Arg
    370                 375                 380
Asn Ser Tyr Val Arg Leu Arg His Leu Cys Thr Asn Thr Trp Val His
385                 390                 395                 400
Ser Thr Asn Ile Pro Ile Asp Lys Glu Glu Glu Lys Pro Val Met Leu
                405                 410                 415
Lys Ile Gly Thr Ser Pro Leu Lys Glu Asp Lys Glu Ala Phe Ala Ile
            420                 425                 430
Val Pro Val Ser Pro Ala Glu Val Arg Asp Leu Asp Phe Ala Asn Asp
        435                 440                 445
Ala Ser Lys Val Leu Gly Ser Ile Ala Gly Lys Leu Glu Lys Gly Thr
    450                 455                 460
Ile Thr Gln Asn Glu Arg Arg Ser Val Thr Lys Leu Leu Glu Asp Leu
465                 470                 475                 480
Val Tyr Phe Val Thr Gly Gly Thr Asn Ser Gly Gln Asp Val Leu Glu
                485                 490                 495
Val Val Phe Ser Lys Pro Asn Arg Glu Arg Gln Lys Leu Met Arg Glu
            500                 505                 510
Gln Asn Ile Leu Lys Gln Ile Phe Lys Leu Leu Gln Ala Pro Phe Thr
        515                 520                 525
Asp Cys Gly Asp Gly Pro Met Leu Arg Leu Glu Glu Leu Gly Asp Gln
    530                 535                 540
```

```
Arg His Ala Pro Phe Arg His Ile Cys Arg Leu Cys Tyr Arg Val Leu
545                 550                 555                 560
Arg His Ser Gln Gln Asp Tyr Arg Lys Asn Gln Glu Tyr Ile Ala Lys
                565                 570                 575
Gln Phe Gly Phe Met Gln Lys Gln Ile Gly Tyr Asp Val Leu Ala Glu
            580                 585                 590
Asp Thr Ile Thr Ala Leu Leu His Asn Asn Arg Lys Leu Leu Glu Lys
        595                 600                 605
His Ile Thr Ala Ala Glu Ile Asp Thr Phe Val Ser Leu Val Arg Lys
    610                 615                 620
Asn Arg Glu Pro Arg Phe Leu Asp Tyr Leu Ser Asp Leu Cys Val Ser
625                 630                 635                 640
Met Asn Lys Ser Ile Pro Val Thr Gln Glu Leu Ile Cys Lys Ala Val
                645                 650                 655
Leu Asn Pro Thr Asn Ala Asp Ile Leu Ile Glu Thr Lys Leu Val Leu
            660                 665                 670
Ser Arg Phe Glu Phe Glu Gly Val Ser Thr Gly Glu Asn Ala Leu Glu
        675                 680                 685
Ala Gly Glu Asp Glu Glu Glu Val Trp Leu Phe Trp Arg Asp Ser Asn
    690                 695                 700
Lys Glu Ile Arg Ser Lys Ser Val Arg Glu Leu Ala Gln Asp Ala Lys
705                 710                 715                 720
Glu Gly Gln Lys Glu Asp Arg Asp Val Leu Ser Tyr Tyr Arg Tyr Gln
                725                 730                 735
Leu Asn Leu Phe Ala Arg Met Cys Leu Asp Arg Gln Tyr Leu Ala Ile
            740                 745                 750
Asn Glu Ile Ser Gly Gln Leu Asp Val Asp Leu Ile Leu Arg Cys Met
        755                 760                 765
Ser Asp Glu Asn Leu Pro Tyr Asp Leu Arg Ala Ser Phe Cys Arg Leu
    770                 775                 780
Met Leu His Met His Val Asp Arg Asp Pro Gln Glu Gln Val Thr Pro
785                 790                 795                 800
Val Lys Tyr Ala Arg Leu Trp Ser Glu Ile Pro Ser Glu Ile Ala Ile
                805                 810                 815
Asp Asp Tyr Asp Ser Ser Gly Ala Ser Lys Asp Glu Ile Lys Glu Arg
            820                 825                 830
Phe Ala Gln Thr Met Glu Phe Val Glu Glu Tyr Leu Arg Asp Val Val
        835                 840                 845
Cys Gln Arg Phe Pro Phe Ser Asp Lys Glu Lys Asn Lys Leu Thr Phe
    850                 855                 860
Glu Val Val Asn Leu Ala Arg Asn Leu Ile Tyr Phe Gly Phe Tyr Asn
865                 870                 875                 880
Phe Ser Asp Leu Leu Arg Leu Thr Lys Ile Leu Leu Ala Ile Leu Asp
                885                 890                 895
Cys Val His Val Thr Thr Ile Phe Pro Ile Ser Lys Met Thr Lys Gly
            900                 905                 910
Glu Glu Asn Lys Gly Ser Asn Val Met Arg Ser Ile His Gly Val Gly
        915                 920                 925
Glu Leu Met Thr Gln Val Val Leu Arg Gly Gly Gly Phe Leu Pro Met
    930                 935                 940
Thr Pro Met Ala Ala Ala Pro Glu Gly Asn Val Lys Gln Ala Glu Pro
945                 950                 955                 960
Glu Lys Glu Asp Ile Met Val Met Asp Thr Lys Leu Lys Ile Ile Glu
                965                 970                 975
Ile Leu Gln Phe Ile Leu Asn Val Arg Leu Asp Tyr Arg Ile Ser Cys
            980                 985                 990
Leu Leu Cys Ile Phe Lys Arg Glu Phe Asp Glu Ser Asn Ser Gln Ser
        995                 1000                1005
Ser Glu Thr Ser Ser Gly Asn Ser Ser Gln Glu Gly Pro Ser Asn Val
    1010                1015                1020
```

```
Pro Gly Ala Leu Asp Phe Glu His Ile Glu Glu Gln Ala Glu Gly Ile
1025                1030                1035                1040
Phe Gly Gly Ser Glu Glu Asn Thr Pro Leu Asp Leu Asp Asp His Gly
                1045                1050                1055
Gly Arg Thr Phe Leu Arg Val Leu Leu His Leu Thr Met His Asp Tyr
            1060                1065                1070
Pro Pro Leu Val Ser Gly Ala Leu Gln Leu Leu Phe Arg His Phe Ser
        1075                1080                1085
Gln Arg Gln Glu Val Leu Gln Ala Phe Lys Gln Val Gln Leu Leu Val
    1090                1095                1100
Thr Ser Gln Asp Val Asp Asn Tyr Lys Gln Ile Lys Gln Asp Leu Asp
1105                1110                1115                1120
Gln Leu Arg Ser Ile Val Glu Lys Ser Glu Leu Trp Val Tyr Lys Gly
                1125                1130                1135
Gln Gly Pro Asp Glu Pro Met Asp Gly Ala Ser Gly Glu Asn Glu His
            1140                1145                1150
Lys Lys Thr Glu Glu Gly Thr Ser Lys Pro Leu Lys His Glu Ser Thr
        1155                1160                1165
Ser Ser Tyr Asn Tyr Arg Val Val Lys Glu Ile Leu Ile Arg Leu Ser
    1170                1175                1180
Lys Leu Cys Val Gln Glu Ser Ala Ser Val Arg Lys Ser Arg Lys Gln
1185                1190                1195                1200
Gln Gln Arg Leu Leu Arg Asn Met Gly Ala His Ala Val Val Leu Glu
                1205                1210                1215
Leu Leu Gln Ile Pro Tyr Glu Lys Ala Glu Asp Thr Lys Met Gln Glu
            1220                1225                1230
Ile Met Arg Leu Ala His Glu Phe Leu Gln Asn Phe Cys Ala Gly Asn
        1235                1240                1245
Gln Gln Asn Gln Ala Leu Leu His Lys His Ile Asn Leu Phe Leu Asn
    1250                1255                1260
Pro Gly Ile Leu Glu Ala Val Thr Met Gln His Ile Phe Met Asn Asn
1265                1270                1275                1280
Phe Gln Leu Cys Ser Glu Ile Asn Glu Arg Val Val Gln His Phe Val
                1285                1290                1295
His Cys Ile Glu Thr His Gly Arg Asn Val Gln Tyr Ile Lys Phe Leu
            1300                1305                1310
Gln Thr Ile Val Lys Ala Glu Gly Lys Phe Ile Lys Lys Cys Gln Asp
        1315                1320                1325
Met Val Met Ala Glu Leu Val Asn Ser Gly Glu Asp Val Leu Val Phe
    1330                1335                1340
Tyr Asn Asp Arg Ala Ser Phe Gln Thr Leu Ile Gln Met Met Arg Ser
1345                1350                1355                1360
Glu Arg Asp Arg Met Asp Glu Asn Ser Pro Leu Phe Met Tyr His Ile
                1365                1370                1375
His Leu Val Glu Leu Leu Ala Val Cys Thr Glu Gly Lys Asn Val Tyr
            1380                1385                1390
Thr Glu Ile Lys Cys Asn Ser Leu Leu Pro Leu Asp Asp Ile Val Arg
        1395                1400                1405
Val Val Thr His Glu Asp Cys Ile Pro Glu Val Lys Ile Ala Tyr Ile
    1410                1415                1420
Asn Phe Leu Asn His Cys Tyr Val Asp Thr Glu Val Glu Met Lys Glu
1425                1430                1435                1440
Ile Tyr Thr Ser Asn His Met Trp Lys Leu Phe Glu Asn Phe Leu Val
                1445                1450                1455
Asp Ile Cys Arg Ala Cys Asn Asn Thr Ser Asp Arg Lys His Ala Asp
            1460                1465                1470
Ser Val Leu Glu Lys Tyr Val Thr Glu Ile Val Met Ser Ile Val Thr
        1475                1480                1485
Thr Phe Phe Ser Ser Pro Phe Ser Asp Gln Ser Thr Thr Leu Gln Thr
    1490                1495                1500
```

```
Arg Gln Pro Val Phe Val Gln Leu Leu Gln Gly Val Phe Arg Val Tyr
1505                1510                1515                1520
His Cys Asn Trp Leu Met Pro Ser Gln Lys Ala Ser Val Glu Ser Cys
                1525                1530                1535
Ile Arg Val Leu Ser Asp Val Ala Lys Ser Arg Ala Ile Ala Ile Pro
            1540                1545                1550
Val Asp Leu Asp Ser Gln Val Asn Asn Leu Phe Leu Lys Ser His Asn
        1555                1560                1565
Ile Val Gln Lys Thr Ala Met Asn Trp Arg Leu Ser Ala Arg Asn Ala
    1570                1575                1580
Ala Arg Arg Asp Ser Val Leu Ala Ala Ser Arg Asp Tyr Arg Asn Ile
1585                1590                1595                1600
Ile Glu Arg Leu Gln Asp Ile Val Ser Ala Leu Glu Asp Arg Leu Arg
                1605                1610                1615
Pro Leu Val Gln Ala Glu Leu Ser Val Leu Val Asp Val Leu His Arg
            1620                1625                1630
Pro Glu Leu Leu Phe Pro Glu Asn Thr Asp Ala Arg Arg Lys Cys Glu
        1635                1640                1645
Ser Gly Gly Phe Ile Cys Lys Leu Ile Lys His Thr Lys Gln Leu Leu
    1650                1655                1660
Glu Glu Asn Glu Glu Lys Leu Cys Ile Lys Val Leu Gln Thr Leu Arg
1665                1670                1675                1680
Glu Met Met Thr Lys Asp Arg Gly Tyr Gly Glu Lys Gln Ile Ser Ile
                1685                1690                1695
Asp Glu Leu Glu Asn Ala Glu Leu Pro Gln Pro Pro Glu Ala Glu Asn
            1700                1705                1710
Ser Thr Glu Glu Leu Glu Pro Ser Pro Pro Leu Arg Gln Leu Glu Asp
        1715                1720                1725
His Lys Arg Gly Glu Ala Leu Arg Gln Ile Leu Val Asn Arg Tyr Tyr
    1730                1735                1740
Gly Asn Ile Arg Pro Ser Gly Arg Arg Glu Glu Leu Thr Ser Phe Gly
1745                1750                1755                1760
Asn Gly Pro Leu Ser Pro Gly Gly Pro Ser Lys Pro Gly Gly Gly Gly
                1765                1770                1775
Gly Gly Pro Gly Ser Gly Ser Thr Ser Arg Gly Glu Met Ser Leu Ala
            1780                1785                1790
Glu Val Gln Cys His Leu Asp Lys Glu Gly Ala Ser Asn Leu Val Ile
        1795                1800                1805
Asp Leu Ile Met Asn Ala Ser Ser Asp Arg Val Phe His Glu Ser Ile
    1810                1815                1820
Leu Leu Ala Ile Ala Leu Leu Glu Gly Gly Asn Thr Thr Ile Gln His
1825                1830                1835                1840
Ser Phe Phe Cys Arg Leu Thr Glu Asp Lys Lys Ser Glu Lys Phe Phe
                1845                1850                1855
Lys Val Phe Tyr Asp Arg Met Lys Val Ala Gln Gln Glu Ile Lys Ala
            1860                1865                1870
Thr Val Thr Val Asn Thr Ser Asp Leu Gly Asn Lys Lys Lys Asp Asp
        1875                1880                1885
Glu Val Asp Arg Asp Ala Pro Ser Arg Lys Lys Ala Lys Glu Pro Thr
    1890                1895                1900
Thr Gln Ile Thr Glu Glu Val Arg Asp Gln Leu Leu Glu Ala Ser Ala
1905                1910                1915                1920
Ala Thr Arg Lys Ala Phe Thr Thr Phe Arg Arg Glu Ala Asp Pro Asp
                1925                1930                1935
Asp His Tyr Gln Ser Gly Glu Gly Thr Gln Ala Thr Thr Asp Lys Ala
            1940                1945                1950
Lys Asp Asp Leu Glu Met Ser Ala Val Ile Thr Ile Met Gln Pro Ile
        1955                1960                1965
Leu Arg Phe Leu Gln Leu Leu Cys Glu Asn His Asn Arg Asp Leu Gln
    1970                1975                1980
```

```
Asn Phe Leu Arg Cys Gln Asn Asn Lys Thr Asn Tyr Asn Leu Val Cys
1985                1990                1995                2000
Glu Thr Leu Gln Phe Leu Asp Cys Ile Cys Gly Ser Thr Thr Gly Gly
                    2005                2010                2015
Leu Gly Leu Leu Gly Leu Tyr Ile Asn Glu Lys Asn Val Ala Leu Ile
            2020                2025                2030
Asn Gln Thr Leu Glu Ser Leu Thr Glu Tyr Cys Gln Gly Pro Cys His
        2035                2040                2045
Glu Asn Gln Asn Cys Ile Ala Thr His Glu Ser Asn Gly Ile Asp Ile
    2050                2055                2060
Ile Thr Ala Leu Ile Leu Asn Asp Ile Asn Pro Leu Gly Lys Lys Arg
2065                2070                2075                2080
Met Asp Leu Val Leu Glu Leu Lys Asn Asn Ala Ser Lys Leu Leu Leu
                    2085                2090                2095
Ala Ile Met Glu Ser Arg His Asp Ser Glu Asn Ala Glu Arg Ile Leu
            2100                2105                2110
Tyr Asn Met Arg Pro Lys Glu Leu Val Glu Val Ile Lys Lys Ala Tyr
        2115                2120                2125
Met Gln Gly Glu Val Glu Phe Glu Asp Gly Glu Asn Gly Glu Asp Gly
    2130                2135                2140
Ala Ala Ser Pro Arg Asn Val Gly His Asn Ile Tyr Ile Leu Ala His
2145                2150                2155                2160
Gln Leu Ala Arg His Asn Lys Glu Leu Gln Thr Met Leu Lys Pro Gly
                    2165                2170                2175
Gly Gln Val Asp Gly Asp Glu Ala Leu Glu Phe Tyr Ala Lys His Thr
            2180                2185                2190
Ala Gln Ile Glu Ile Val Arg Leu Asp Arg Thr Met Glu Gln Ile Val
        2195                2200                2205
Phe Pro Val Pro Ser Ile Cys Glu Phe Leu Thr Lys Glu Ser Lys Leu
    2210                2215                2220
Arg Ile Tyr Tyr Thr Thr Glu Arg Asp Glu Gln Gly Ser Lys Ile Asn
2225                2230                2235                2240
Asp Phe Phe Leu Arg Ser Glu Asp Leu Phe Asn Glu Met Asn Trp Gln
                    2245                2250                2255
Lys Lys Leu Arg Ala Gln Pro Val Leu Tyr Trp Cys Ala Arg Asn Met
            2260                2265                2270
Ser Phe Trp Ser Ser Ile Ser Phe Asn Leu Ala Val Leu Met Asn Leu
        2275                2280                2285
Leu Val Ala Phe Phe Tyr Pro Phe Lys Gly Val Arg Gly Gly Thr Leu
    2290                2295                2300
Glu Pro His Trp Ser Gly Leu Leu Trp Thr Ala Met Leu Ile Ser Leu
2305                2310                2315                2320
Ala Ile Val Ile Ala Leu Pro Lys Pro His Gly Ile Arg Ala Leu Ile
                    2325                2330                2335
Ala Ser Thr Ile Leu Arg Leu Ile Phe Ser Val Gly Leu Gln Pro Thr
            2340                2345                2350
Leu Phe Leu Leu Gly Ala Phe Asn Val Cys Asn Lys Ile Ile Phe Leu
        2355                2360                2365
Met Ser Phe Val Gly Asn Cys Gly Thr Phe Thr Arg Gly Tyr Arg Ala
    2370                2375                2380
Met Val Leu Asp Val Glu Phe Leu Tyr His Leu Leu Tyr Leu Leu Ile
2385                2390                2395                2400
Cys Ala Met Gly Leu Phe Val His Glu Phe Phe Tyr Ser Leu Leu Leu
                    2405                2410                2415
Phe Asp Leu Val Tyr Arg Glu Glu Thr Leu Leu Asn Val Ile Lys Ser
            2420                2425                2430
Val Thr Arg Asn Gly Arg Pro Ile Ile Leu Thr Ala Ala Leu Ala Leu
        2435                2440                2445
Ile Leu Val Tyr Leu Phe Ser Ile Val Gly Tyr Leu Phe Phe Lys Asp
    2450                2455                2460
```

```
Asp Phe Ile Leu Glu Val Asp Arg Leu Pro Asn Glu Thr Ala Gly Pro
2465                2470                2475                2480
Glu Thr Gly Glu Ser Leu Ala Asn Asp Phe Leu Tyr Ser Asp Val Cys
                2485                2490                2495
Arg Val Glu Thr Gly Glu Asn Cys Thr Ser Pro Ala Pro Lys Glu Glu
            2500                2505                2510
Leu Leu Pro Val Glu Glu Thr Glu Gln Asp Lys Glu His Thr Cys Glu
        2515                2520                2525
Thr Leu Leu Met Cys Ile Val Thr Val Leu Ser His Gly Leu Arg Ser
    2530                2535                2540
Gly Gly Gly Val Gly Asp Val Leu Arg Lys Pro Ser Lys Glu Glu Pro
2545                2550                2555                2560
Leu Phe Ala Ala Arg Val Ile Tyr Asp Leu Leu Phe Phe Phe Met Val
                2565                2570                2575
Ile Ile Ile Val Leu Asn Leu Ile Phe Gly Val Ile Ile Asp Thr Phe
            2580                2585                2590
Ala Asp Leu Arg Ser Glu Lys Gln Lys Lys Glu Glu Ile Leu Lys Thr
        2595                2600                2605
Thr Cys Phe Ile Cys Gly Leu Glu Arg Asp Lys Phe Asp Asn Lys Thr
    2610                2615                2620
Val Thr Phe Glu Glu His Ile Lys Glu Glu His Asn Met Trp His Tyr
2625                2630                2635                2640
Leu Cys Phe Ile Val Leu Val Lys Val Lys Asp Ser Thr Glu Tyr Thr
                2645                2650                2655
Gly Pro Glu Ser Tyr Val Ala Glu Met Ile Arg Glu Arg Asn Leu Asp
            2660                2665                2670
Trp Phe Pro Arg Met Arg Ala Met Ser Leu Val Ser Ser Asp Ser Glu
        2675                2680                2685
Gly Glu Gln Asn Glu Leu Arg Asn Leu Gln Glu Lys Leu Glu Ser Thr
    2690                2695                2700
Met Lys Leu Val Thr Asn Leu Ser Gly Gln Leu Ser Glu Leu Lys Asp
2705                2710                2715                2720
Gln Met Thr Glu Gln Arg Lys Gln Lys Gln Arg Ile Gly Leu Leu Gly
                2725                2730                2735
His Pro Pro His Met Asn Val Asn Pro Gln Gln Pro Ala
            2740                2745


<210> 7
<211> 2710
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/note =
      synthetic construct

<400> 7
Met Ser Asp Lys Met Ser Ser Phe Leu His Ile Gly Asp Ile Cys Ser
 1               5                  10                  15
Leu Tyr Ala Glu Gly Ser Thr Asn Gly Phe Ile Ser Thr Leu Gly Leu
            20                  25                  30
Val Asp Asp Arg Cys Val Val Gln Pro Glu Ala Gly Asp Leu Asn Asn
        35                  40                  45
Pro Pro Lys Lys Phe Arg Asp Cys Leu Phe Lys Leu Cys Pro Met Asn
    50                  55                  60
Arg Tyr Ser Ala Gln Lys Gln Phe Trp Lys Ala Ala Lys Pro Gly Ala
65                  70                  75                  80
Asn Ser Thr Thr Asp Ala Val Leu Leu Asn Lys Leu His His Ala Ala
                85                  90                  95
```

```
Asp Leu Glu Lys Lys Gln Asn Glu Thr Glu Asn Arg Lys Leu Leu Gly
            100                 105                 110
Thr Val Ile Gln Tyr Gly Asn Val Ile Gln Leu Leu His Leu Lys Ser
        115                 120                 125
Asn Lys Tyr Leu Thr Val Asn Lys Arg Leu Pro Ala Leu Leu Glu Lys
    130                 135                 140
Asn Ala Met Arg Val Thr Leu Asp Glu Ala Gly Asn Glu Gly Ser Trp
145                 150                 155                 160
Phe Tyr Ile Gln Pro Phe Tyr Lys Leu Arg Ser Ile Gly Asp Ser Val
                165                 170                 175
Val Ile Gly Asp Lys Val Val Leu Asn Pro Val Asn Ala Gly Gln Pro
            180                 185                 190
Leu His Ala Ser Ser His Gln Leu Val Asp Asn Pro Gly Cys Asn Glu
        195                 200                 205
Val Asn Ser Val Asn Cys Asn Thr Ser Trp Lys Ile Val Leu Phe Met
    210                 215                 220
Lys Trp Ser Asp Asn Lys Asp Asp Ile Leu Lys Gly Gly Asp Val Val
225                 230                 235                 240
Arg Leu Phe His Ala Glu Gln Glu Lys Phe Leu Thr Cys Asp Glu His
                245                 250                 255
Arg Lys Lys Gln His Val Phe Leu Arg Thr Thr Gly Arg Gln Ser Ala
            260                 265                 270
Thr Ser Ala Thr Ser Ser Lys Ala Leu Trp Glu Val Glu Val Val Gln
        275                 280                 285
His Asp Pro Cys Arg Gly Gly Ala Gly Tyr Trp Asn Ser Leu Phe Arg
    290                 295                 300
Phe Lys His Leu Ala Thr Gly His Tyr Leu Ala Ala Glu Val Asp Pro
305                 310                 315                 320
Asp Phe Glu Glu Glu Cys Leu Glu Phe Gln Pro Ser Val Asp Pro Asp
                325                 330                 335
Gln Asp Ala Ser Arg Ser Arg Leu Arg Asn Ala Gln Glu Lys Met Val
            340                 345                 350
Tyr Ser Leu Val Ser Val Pro Glu Gly Asn Asp Ile Ser Ser Ile Phe
        355                 360                 365
Glu Leu Asp Pro Thr Thr Leu Arg Gly Gly Asp Ser Leu Val Pro Arg
    370                 375                 380
Asn Ser Tyr Val Arg Leu Arg His Leu Cys Thr Asn Thr Trp Val His
385                 390                 395                 400
Ser Thr Asn Ile Pro Ile Asp Lys Glu Glu Glu Lys Pro Val Met Leu
                405                 410                 415
Lys Ile Gly Thr Ser Pro Leu Lys Glu Asp Lys Glu Ala Phe Ala Ile
            420                 425                 430
Val Pro Val Ser Pro Ala Glu Val Arg Asp Leu Asp Phe Ala Asn Asp
        435                 440                 445
Ala Ser Lys Val Leu Gly Ser Ile Ala Gly Lys Leu Glu Lys Gly Thr
    450                 455                 460
Ile Thr Gln Asn Glu Arg Arg Ser Val Thr Lys Leu Leu Glu Asp Leu
465                 470                 475                 480
Val Tyr Phe Val Thr Gly Gly Thr Asn Ser Gly Gln Asp Val Leu Glu
                485                 490                 495
Val Val Phe Ser Lys Pro Asn Arg Glu Arg Gln Lys Leu Met Arg Glu
            500                 505                 510
Gln Asn Ile Leu Lys Gln Ile Phe Lys Leu Leu Gln Ala Pro Phe Thr
        515                 520                 525
Asp Cys Gly Asp Gly Pro Met Leu Arg Leu Glu Glu Leu Gly Asp Gln
    530                 535                 540
Arg His Ala Pro Phe Arg His Ile Cys Arg Leu Cys Tyr Arg Val Leu
545                 550                 555                 560
Arg His Ser Gln Gln Asp Tyr Arg Lys Asn Gln Glu Tyr Ile Ala Lys
                565                 570                 575
```

```
Gln Phe Gly Phe Met Gln Lys Gln Ile Gly Tyr Asp Val Leu Ala Glu
            580                 585                 590
Asp Thr Ile Thr Ala Leu Leu His Asn Asn Arg Lys Leu Leu Glu Lys
        595                 600                 605
His Ile Thr Ala Ala Glu Ile Asp Thr Phe Val Ser Leu Val Arg Lys
    610                 615                 620
Asn Arg Glu Pro Arg Phe Leu Asp Tyr Leu Ser Asp Leu Cys Val Ser
625                 630                 635                 640
Met Asn Lys Ser Ile Pro Val Thr Gln Glu Leu Ile Cys Lys Ala Val
                645                 650                 655
Leu Asn Pro Thr Asn Ala Asp Ile Leu Ile Glu Thr Lys Leu Val Leu
            660                 665                 670
Ser Arg Phe Glu Phe Glu Gly Val Ser Thr Gly Glu Asn Ala Leu Glu
        675                 680                 685
Ala Gly Glu Asp Glu Glu Glu Val Trp Leu Phe Trp Arg Asp Ser Asn
    690                 695                 700
Lys Glu Ile Arg Ser Lys Ser Val Arg Glu Leu Ala Gln Asp Ala Lys
705                 710                 715                 720
Glu Gly Gln Lys Glu Asp Arg Asp Val Leu Ser Tyr Tyr Arg Tyr Gln
                725                 730                 735
Leu Asn Leu Phe Ala Arg Met Cys Leu Asp Arg Gln Tyr Leu Ala Ile
            740                 745                 750
Asn Glu Ile Ser Gly Gln Leu Asp Val Asp Leu Ile Leu Arg Cys Met
        755                 760                 765
Ser Asp Glu Asn Leu Pro Tyr Asp Leu Arg Ala Ser Phe Cys Arg Leu
    770                 775                 780
Met Leu His Met His Val Asp Arg Asp Pro Gln Glu Gln Val Thr Pro
785                 790                 795                 800
Val Lys Tyr Ala Arg Leu Trp Ser Glu Ile Pro Ser Glu Ile Ala Ile
                805                 810                 815
Asp Asp Tyr Asp Ser Ser Gly Ala Ser Lys Asp Glu Ile Lys Glu Arg
            820                 825                 830
Phe Ala Gln Thr Met Glu Phe Val Glu Glu Tyr Leu Arg Asp Val Val
        835                 840                 845
Cys Gln Arg Phe Pro Phe Ser Asp Lys Glu Lys Asn Lys Leu Thr Phe
    850                 855                 860
Glu Val Val Asn Leu Ala Arg Asn Leu Ile Tyr Phe Gly Phe Tyr Asn
865                 870                 875                 880
Phe Ser Asp Leu Leu Arg Leu Thr Lys Ile Leu Leu Ala Ile Leu Asp
                885                 890                 895
Cys Val His Val Thr Thr Ile Phe Pro Ile Ser Lys Met Thr Lys Gly
            900                 905                 910
Glu Glu Asn Lys Gly Ser Asn Val Met Arg Ser Ile His Gly Val Gly
        915                 920                 925
Glu Leu Met Thr Gln Val Val Leu Arg Gly Gly Gly Phe Leu Pro Met
    930                 935                 940
Thr Pro Met Ala Ala Ala Pro Glu Gly Asn Val Lys Gln Ala Glu Pro
945                 950                 955                 960
Glu Lys Glu Asp Ile Met Val Met Asp Thr Lys Leu Lys Ile Ile Glu
                965                 970                 975
Ile Leu Gln Phe Ile Leu Asn Val Arg Leu Asp Tyr Arg Ile Ser Cys
            980                 985                 990
Leu Leu Cys Ile Phe Lys Arg Glu Phe Asp Glu Ser Asn Ser Gln Ser
        995                 1000                1005
Ser Glu Thr Ser Ser Gly Asn Ser Ser Gln Glu Gly Pro Ser Asn Val
    1010                1015                1020
Pro Gly Ala Leu Asp Phe Glu His Ile Glu Glu Gln Ala Glu Gly Ile
1025                1030                1035                1040
Phe Gly Gly Ser Glu Glu Asn Thr Pro Leu Asp Leu Asp Asp His Gly
                1045                1050                1055
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Gly Arg Thr Phe Leu Arg Val Leu Leu His Leu Thr Met His Asp Tyr
1060 1065 1070
Pro Pro Leu Val Ser Gly Ala Leu Gln Leu Leu Phe Arg His Phe Ser
1075 1080 1085
Gln Arg Gln Glu Val Leu Gln Ala Phe Lys Gln Val Gln Leu Leu Val
1090 1095 1100
Thr Ser Gln Asp Val Asp Asn Tyr Lys Gln Ile Lys Gln Asp Leu Asp
1105 1110 1115 1120
Gln Leu Arg Ser Ile Val Glu Lys Ser Glu Leu Trp Val Tyr Lys Gly
1125 1130 1135
Gln Gly Pro Asp Glu Pro Met Asp Gly Ala Ser Gly Glu Asn Glu His
1140 1145 1150
Lys Lys Thr Glu Glu Gly Thr Ser Lys Pro Leu Lys His Glu Ser Thr
1155 1160 1165
Ser Ser Tyr Asn Tyr Arg Val Val Lys Glu Ile Leu Ile Arg Leu Ser
1170 1175 1180
Lys Leu Cys Val Gln Glu Ser Ala Ser Val Arg Lys Ser Arg Lys Gln
1185 1190 1195 1200
Gln Gln Arg Leu Leu Arg Asn Met Gly Ala His Ala Val Val Leu Glu
1205 1210 1215
Leu Leu Gln Ile Pro Tyr Glu Lys Ala Glu Asp Thr Lys Met Gln Glu
1220 1225 1230
Ile Met Arg Leu Ala His Glu Phe Leu Gln Asn Phe Cys Ala Gly Asn
1235 1240 1245
Gln Gln Asn Gln Ala Leu Leu His Lys His Ile Asn Leu Phe Leu Asn
1250 1255 1260
Pro Gly Ile Leu Glu Ala Val Thr Met Gln His Ile Phe Met Asn Asn
1265 1270 1275 1280
Phe Gln Leu Cys Ser Glu Ile Asn Glu Arg Val Val Gln His Phe Val
1285 1290 1295
His Cys Ile Glu Thr His Gly Arg Asn Val Gln Tyr Ile Lys Phe Leu
1300 1305 1310
Gln Thr Ile Val Lys Ala Glu Gly Lys Phe Ile Lys Lys Cys Gln Asp
1315 1320 1325
Met Val Met Ala Glu Leu Val Asn Ser Gly Glu Asp Val Leu Val Phe
1330 1335 1340
Tyr Asn Asp Arg Ala Ser Phe Gln Thr Leu Ile Gln Met Met Arg Ser
1345 1350 1355 1360
Glu Arg Asp Arg Met Asp Glu Asn Ser Pro Leu Phe Met Tyr His Ile
1365 1370 1375
His Leu Val Glu Leu Leu Ala Val Cys Thr Glu Gly Lys Asn Val Tyr
1380 1385 1390
Thr Glu Ile Lys Cys Asn Ser Leu Leu Pro Leu Asp Asp Ile Val Arg
1395 1400 1405
Val Val Thr His Glu Asp Cys Ile Pro Glu Val Lys Ile Ala Tyr Ile
1410 1415 1420
Asn Phe Leu Asn His Cys Tyr Val Asp Thr Glu Val Glu Met Lys Glu
1425 1430 1435 1440
Ile Tyr Thr Ser Asn His Met Trp Lys Leu Phe Glu Asn Phe Leu Val
1445 1450 1455
Asp Ile Cys Arg Ala Cys Asn Asn Thr Ser Asp Arg Lys His Ala Asp
1460 1465 1470
Ser Val Leu Glu Lys Tyr Val Thr Glu Ile Val Met Ser Ile Val Thr
1475 1480 1485
Thr Phe Phe Ser Ser Pro Phe Ser Asp Gln Ser Thr Thr Leu Gln Thr
1490 1495 1500
Arg Gln Pro Val Phe Val Gln Leu Leu Gln Gly Val Phe Arg Val Tyr
1505 1510 1515 1520
His Cys Asn Trp Leu Met Pro Ser Gln Lys Ala Ser Val Glu Ser Cys
1525 1530 1535

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Ile Arg Val Leu Ser Asp Val Ala Lys Ser Arg Ala Ile Ala Ile Pro
            1540                1545                1550
Val Asp Leu Asp Ser Gln Val Asn Asn Leu Phe Leu Lys Ser His Asn
        1555                1560                1565
Ile Val Gln Lys Thr Ala Met Asn Trp Arg Leu Ser Ala Arg Asn Ala
    1570                1575                1580
Ala Arg Arg Asp Ser Val Leu Ala Ala Ser Arg Asp Tyr Arg Asn Ile
1585                1590                1595                1600
Ile Glu Arg Leu Gln Asp Ile Val Ser Ala Leu Glu Asp Arg Leu Arg
                1605                1610                1615
Pro Leu Val Gln Ala Glu Leu Ser Val Leu Val Asp Val Leu His Arg
            1620                1625                1630
Pro Glu Leu Leu Phe Pro Glu Asn Thr Asp Ala Arg Arg Lys Cys Glu
        1635                1640                1645
Ser Gly Gly Phe Ile Cys Lys Leu Ile Lys His Thr Lys Gln Leu Leu
    1650                1655                1660
Glu Glu Asn Glu Glu Lys Leu Cys Ile Lys Val Leu Gln Thr Leu Arg
1665                1670                1675                1680
Glu Met Met Thr Lys Asp Arg Gly Tyr Gly Glu Lys Gly Glu Ala Leu
                1685                1690                1695
Arg Gln Ile Leu Val Asn Arg Tyr Tyr Gly Asn Ile Arg Pro Ser Gly
            1700                1705                1710
Arg Arg Glu Asp Leu Thr Ser Phe Gly Asn Gly Pro Leu Ser Pro Gly
        1715                1720                1725
Gly Pro Ser Lys Pro Gly Gly Gly Gly Gly Gly Pro Gly Ser Gly Ser
    1730                1735                1740
Thr Ser Arg Gly Glu Met Ser Leu Ala Glu Val Gln Cys His Leu Asp
1745                1750                1755                1760
Lys Glu Gly Ala Ser Asn Leu Val Ile Asp Leu Ile Met Asn Ala Ser
                1765                1770                1775
Ser Asp Arg Val Phe His Glu Ser Ile Leu Leu Ala Ile Ala Leu Leu
            1780                1785                1790
Glu Gly Gly Asn Thr Thr Ile Gln His Ser Phe Phe Cys Arg Leu Thr
        1795                1800                1805
Glu Asp Lys Lys Ser Glu Lys Phe Phe Lys Val Phe Tyr Asp Arg Met
    1810                1815                1820
Lys Val Ala Gln Gln Glu Ile Lys Ala Thr Val Thr Val Asn Thr Ser
1825                1830                1835                1840
Asp Leu Gly Asn Lys Lys Lys Asp Asp Glu Val Asp Arg Asp Ala Pro
                1845                1850                1855
Ser Arg Lys Lys Ala Lys Glu Pro Thr Thr Gln Ile Thr Glu Glu Val
            1860                1865                1870
Arg Asp Gln Leu Leu Glu Ala Ser Ala Ala Thr Arg Lys Ala Phe Thr
        1875                1880                1885
Thr Phe Arg Arg Glu Ala Asp Pro Asp Asp His Tyr Gln Ser Gly Glu
    1890                1895                1900
Gly Thr Gln Ala Thr Thr Asp Lys Ala Lys Asp Asp Leu Glu Met Ser
1905                1910                1915                1920
Ala Val Ile Thr Ile Met Gln Pro Ile Leu Arg Phe Leu Gln Leu Leu
                1925                1930                1935
Cys Glu Asn His Asn Arg Asp Leu Gln Asn Phe Leu Arg Cys Gln Asn
            1940                1945                1950
Asn Lys Thr Asn Tyr Asn Leu Val Cys Glu Thr Leu Gln Phe Leu Asp
        1955                1960                1965
Cys Ile Cys Gly Ser Thr Thr Gly Gly Leu Gly Leu Leu Gly Leu Tyr
    1970                1975                1980
Ile Asn Glu Lys Asn Val Ala Leu Ile Asn Gln Thr Leu Glu Ser Leu
1985                1990                1995                2000
Thr Glu Tyr Cys Gln Gly Pro Cys His Glu Asn Gln Asn Cys Ile Ala
                2005                2010                2015
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Thr His Glu Ser Asn Gly Ile Asp Ile Ile Thr Ala Leu Ile Leu Asn
            2020                2025                2030
Asp Ile Asn Pro Leu Gly Lys Lys Arg Met Asp Leu Val Leu Glu Leu
        2035                2040                2045
Lys Asn Asn Ala Ser Lys Leu Leu Leu Ala Ile Met Glu Ser Arg His
    2050                2055                2060
Asp Ser Glu Asn Ala Glu Arg Ile Leu Tyr Asn Met Arg Pro Lys Glu
2065                2070                2075                2080
Leu Val Glu Val Ile Lys Lys Ala Tyr Met Gln Gly Glu Val Glu Phe
                2085                2090                2095
Glu Asp Gly Glu Asn Gly Glu Asp Gly Ala Ala Ser Pro Arg Asn Val
            2100                2105                2110
Gly His Asn Ile Tyr Ile Leu Ala His Gln Leu Ala Arg His Asn Lys
        2115                2120                2125
Glu Leu Gln Thr Met Leu Lys Pro Gly Gly Gln Val Asp Gly Asp Glu
    2130                2135                2140
Ala Leu Glu Phe Tyr Ala Lys His Thr Ala Gln Ile Glu Ile Val Arg
2145                2150                2155                2160
Leu Asp Arg Thr Met Glu Gln Ile Val Phe Pro Val Pro Ser Ile Cys
                2165                2170                2175
Glu Phe Leu Thr Lys Glu Ser Lys Leu Arg Ile Tyr Tyr Thr Thr Glu
            2180                2185                2190
Arg Asp Glu Gln Gly Ser Lys Ile Asn Asp Phe Phe Leu Arg Ser Glu
        2195                2200                2205
Asp Leu Phe Asn Glu Met Asn Trp Gln Lys Lys Leu Arg Ala Gln Pro
    2210                2215                2220
Val Leu Tyr Trp Cys Ala Arg Asn Met Ser Phe Trp Ser Ser Ile Ser
2225                2230                2235                2240
Phe Asn Leu Ala Val Leu Met Asn Leu Leu Val Ala Phe Phe Tyr Pro
                2245                2250                2255
Phe Lys Gly Val Arg Gly Gly Thr Leu Glu Pro His Trp Ser Gly Leu
            2260                2265                2270
Leu Trp Thr Ala Met Leu Ile Ser Leu Ala Ile Val Ile Ala Leu Pro
        2275                2280                2285
Lys Pro His Gly Ile Arg Ala Leu Ile Ala Ser Thr Ile Leu Arg Leu
    2290                2295                2300
Ile Phe Ser Val Gly Leu Gln Pro Thr Leu Phe Leu Leu Gly Ala Phe
2305                2310                2315                2320
Asn Val Cys Asn Lys Ile Ile Phe Leu Met Ser Phe Val Gly Asn Cys
                2325                2330                2335
Gly Thr Phe Thr Arg Gly Tyr Arg Ala Met Val Leu Asp Val Glu Phe
            2340                2345                2350
Leu Tyr His Leu Leu Tyr Leu Leu Ile Cys Ala Met Gly Leu Phe Val
        2355                2360                2365
His Glu Phe Phe Tyr Ser Leu Leu Leu Phe Asp Leu Val Tyr Arg Glu
    2370                2375                2380
Glu Thr Leu Leu Asn Val Ile Lys Ser Val Thr Arg Asn Gly Arg Pro
2385                2390                2395                2400
Ile Ile Leu Thr Ala Ala Leu Ala Leu Ile Leu Val Tyr Leu Phe Ser
                2405                2410                2415
Ile Val Gly Tyr Leu Phe Phe Lys Asp Asp Phe Ile Leu Glu Val Asp
            2420                2425                2430
Arg Leu Pro Asn Glu Thr Ala Gly Pro Glu Thr Gly Glu Ser Leu Ala
        2435                2440                2445
Asn Asp Phe Leu Tyr Ser Asp Val Cys Arg Val Glu Thr Gly Glu Asn
    2450                2455                2460
Cys Thr Ser Pro Ala Pro Lys Glu Glu Leu Leu Pro Val Glu Glu Thr
2465                2470                2475                2480
Glu Gln Asp Lys Glu His Thr Cys Glu Thr Leu Leu Met Cys Ile Val
                2485                2490                2495
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Thr Val Leu Ser His Gly Leu Arg Ser Gly Gly Gly Val Gly Asp Val
            2500                2505                2510
Leu Arg Lys Pro Ser Lys Glu Glu Pro Leu Phe Ala Ala Arg Val Ile
        2515                2520                2525
Tyr Asp Leu Leu Phe Phe Phe Met Val Ile Ile Ile Val Leu Asn Leu
    2530                2535                2540
Ile Phe Gly Val Ile Ile Asp Thr Phe Ala Asp Leu Arg Ser Glu Lys
2545                2550                2555                2560
Gln Lys Lys Glu Glu Ile Leu Lys Thr Thr Cys Phe Ile Cys Gly Leu
                2565                2570                2575
Glu Arg Asp Lys Phe Asp Asn Lys Thr Val Thr Phe Glu Glu His Ile
            2580                2585                2590
Lys Glu Glu His Asn Met Trp His Tyr Leu Cys Phe Ile Val Leu Val
        2595                2600                2605
Lys Val Lys Asp Ser Thr Glu Tyr Thr Gly Pro Glu Ser Tyr Val Ala
    2610                2615                2620
Glu Met Ile Arg Glu Arg Asn Leu Asp Trp Phe Pro Arg Met Arg Ala
2625                2630                2635                2640
Met Ser Leu Val Ser Ser Asp Ser Glu Gly Glu Gln Asn Glu Leu Arg
                2645                2650                2655
Asn Leu Gln Glu Lys Leu Glu Ser Thr Met Lys Leu Val Thr Asn Leu
            2660                2665                2670
Ser Gly Gln Leu Ser Glu Leu Lys Asp Gln Met Thr Glu Gln Arg Lys
        2675                2680                2685
Gln Lys Gln Arg Ile Gly Leu Leu Gly His Pro Pro His Met Asn Val
    2690                2695                2700
Asn Pro Gln Gln Pro Ala
2705                2710
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<210> 8
<211> 2749
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/note =
synthetic construct

<400> 8

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Met Ser Asp Lys Met Ser Ser Phe Leu His Ile Gly Asp Ile Cys Ser
 1                5                  10                  15
Leu Tyr Ala Glu Gly Ser Thr Asn Gly Phe Ile Ser Thr Leu Gly Leu
            20                  25                  30
Val Asp Asp Arg Cys Val Val Gln Pro Glu Ala Gly Asp Leu Asn Asn
        35                  40                  45
Pro Pro Lys Lys Phe Arg Asp Cys Leu Phe Lys Leu Cys Pro Met Asn
    50                  55                  60
Arg Tyr Ser Ala Gln Lys Gln Phe Trp Lys Ala Ala Lys Pro Gly Ala
65                  70                  75                  80
Asn Ser Thr Thr Asp Ala Val Leu Leu Asn Lys Leu His His Ala Ala
                85                  90                  95
Asp Leu Glu Lys Lys Gln Asn Glu Thr Glu Asn Arg Lys Leu Leu Gly
            100                 105                 110
Thr Val Ile Gln Tyr Gly Asn Val Ile Gln Leu Leu His Leu Lys Ser
        115                 120                 125
Asn Lys Tyr Leu Thr Val Asn Lys Arg Leu Pro Ala Leu Leu Glu Lys
    130                 135                 140
Asn Ala Met Arg Val Thr Leu Asp Glu Ala Gly Asn Glu Gly Ser Trp
145                 150                 155                 160
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Phe Tyr Ile Gln Pro Phe Tyr Lys Leu Arg Ser Ile Gly Asp Ser Val
                165                 170                 175
Val Ile Gly Asp Lys Val Val Leu Asn Pro Val Asn Ala Gly Gln Pro
            180                 185                 190
Leu His Ala Ser Ser His Gln Leu Val Asp Asn Pro Gly Cys Asn Glu
        195                 200                 205
Val Asn Ser Val Asn Cys Asn Thr Ser Trp Lys Ile Val Leu Phe Met
    210                 215                 220
Lys Trp Ser Asp Asn Lys Asp Asp Ile Leu Lys Gly Gly Asp Val Val
225                 230                 235                 240
Arg Leu Phe His Ala Glu Gln Glu Lys Phe Leu Thr Cys Asp Glu His
                245                 250                 255
Arg Lys Lys Gln His Val Phe Leu Arg Thr Thr Gly Arg Gln Ser Ala
            260                 265                 270
Thr Ser Ala Thr Ser Ser Lys Ala Leu Trp Glu Val Glu Val Val Gln
        275                 280                 285
His Asp Pro Cys Arg Gly Gly Ala Gly Tyr Trp Asn Ser Leu Phe Arg
    290                 295                 300
Phe Lys His Leu Ala Thr Gly His Tyr Leu Ala Ala Glu Val Asp Pro
305                 310                 315                 320
Asp Phe Glu Glu Glu Cys Leu Glu Phe Gln Pro Ser Val Asp Pro Asp
                325                 330                 335
Gln Asp Ala Ser Arg Ser Arg Leu Arg Asn Ala Gln Glu Lys Met Val
            340                 345                 350
Tyr Ser Leu Val Ser Val Pro Glu Gly Asn Asp Ile Ser Ser Ile Phe
        355                 360                 365
Glu Leu Asp Pro Thr Thr Leu Arg Gly Gly Asp Ser Leu Val Pro Arg
    370                 375                 380
Asn Ser Tyr Val Arg Leu Arg His Leu Cys Thr Asn Thr Trp Val His
385                 390                 395                 400
Ser Thr Asn Ile Pro Ile Asp Lys Glu Glu Glu Lys Pro Val Met Leu
                405                 410                 415
Lys Ile Gly Thr Ser Pro Leu Lys Glu Asp Lys Glu Ala Phe Ala Ile
            420                 425                 430
Val Pro Val Ser Pro Ala Glu Val Arg Asp Leu Asp Phe Ala Asn Asp
        435                 440                 445
Ala Ser Lys Val Leu Gly Ser Ile Ala Gly Lys Leu Glu Lys Gly Thr
    450                 455                 460
Ile Thr Gln Asn Glu Arg Arg Ser Val Thr Lys Leu Leu Glu Asp Leu
465                 470                 475                 480
Val Tyr Phe Val Thr Gly Gly Thr Asn Ser Gly Gln Asp Val Leu Glu
                485                 490                 495
Val Val Phe Ser Lys Pro Asn Arg Glu Arg Gln Lys Leu Met Arg Glu
            500                 505                 510
Gln Asn Ile Leu Lys Gln Ile Phe Lys Leu Leu Gln Ala Pro Phe Thr
        515                 520                 525
Asp Cys Gly Asp Gly Pro Met Leu Arg Leu Glu Glu Leu Gly Asp Gln
    530                 535                 540
Arg His Ala Pro Phe Arg His Ile Cys Arg Leu Cys Tyr Arg Val Leu
545                 550                 555                 560
Arg His Ser Gln Gln Asp Tyr Arg Lys Asn Gln Glu Tyr Ile Ala Lys
                565                 570                 575
Gln Phe Gly Phe Met Gln Lys Gln Ile Gly Tyr Asp Val Leu Ala Glu
            580                 585                 590
Asp Thr Ile Thr Ala Leu Leu His Asn Asn Arg Lys Leu Leu Glu Lys
        595                 600                 605
His Ile Thr Ala Ala Glu Ile Asp Thr Phe Val Ser Leu Val Arg Lys
    610                 615                 620
Asn Arg Glu Pro Arg Phe Leu Asp Tyr Leu Ser Asp Leu Cys Val Ser
625                 630                 635                 640
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Met Asn Lys Ser Ile Pro Val Thr Gln Glu Leu Ile Cys Lys Ala Val
                645                 650                 655
Leu Asn Pro Thr Asn Ala Asp Ile Leu Ile Glu Thr Lys Leu Val Leu
            660                 665                 670
Ser Arg Phe Glu Phe Glu Gly Val Ser Thr Gly Glu Asn Ala Leu Glu
        675                 680                 685
Ala Gly Glu Asp Glu Glu Glu Val Trp Leu Phe Trp Arg Asp Ser Asn
    690                 695                 700
Lys Glu Ile Arg Ser Lys Ser Val Arg Glu Leu Ala Gln Asp Ala Lys
705                 710                 715                 720
Glu Gly Gln Lys Glu Asp Arg Asp Val Leu Ser Tyr Tyr Arg Tyr Gln
                725                 730                 735
Leu Asn Leu Phe Ala Arg Met Cys Leu Asp Arg Gln Tyr Leu Ala Ile
            740                 745                 750
Asn Glu Ile Ser Gly Gln Leu Asp Val Asp Leu Ile Leu Arg Cys Met
        755                 760                 765
Ser Asp Glu Asn Leu Pro Tyr Asp Leu Arg Ala Ser Phe Cys Arg Leu
    770                 775                 780
Met Leu His Met His Val Asp Arg Asp Pro Gln Glu Gln Val Thr Pro
785                 790                 795                 800
Val Lys Tyr Ala Arg Leu Trp Ser Glu Ile Pro Ser Glu Ile Ala Ile
                805                 810                 815
Asp Asp Tyr Asp Ser Ser Gly Ala Ser Lys Asp Glu Ile Lys Glu Arg
            820                 825                 830
Phe Ala Gln Thr Met Glu Phe Val Glu Glu Tyr Leu Arg Asp Val Val
        835                 840                 845
Cys Gln Arg Phe Pro Phe Ser Asp Lys Glu Lys Asn Lys Leu Thr Phe
    850                 855                 860
Glu Val Val Asn Leu Ala Arg Asn Leu Ile Tyr Phe Gly Phe Tyr Asn
865                 870                 875                 880
Phe Ser Asp Leu Leu Arg Leu Thr Lys Ile Leu Leu Ala Ile Leu Asp
                885                 890                 895
Cys Val His Val Thr Thr Ile Phe Pro Ile Ser Lys Met Thr Lys Gly
            900                 905                 910
Glu Glu Asn Lys Gly Ser Asn Val Met Arg Ser Ile His Gly Val Gly
        915                 920                 925
Glu Leu Met Thr Gln Val Val Leu Arg Gly Gly Gly Phe Leu Pro Met
    930                 935                 940
Thr Pro Met Ala Ala Ala Pro Glu Gly Asn Val Lys Gln Ala Glu Pro
945                 950                 955                 960
Glu Lys Glu Asp Ile Met Val Met Asp Thr Lys Leu Lys Ile Ile Glu
                965                 970                 975
Ile Leu Gln Phe Ile Leu Asn Val Arg Leu Asp Tyr Arg Ile Ser Cys
            980                 985                 990
Leu Leu Cys Ile Phe Lys Arg Glu Phe Asp Glu Ser Asn Ser Gln Ser
        995                1000                1005
Ser Glu Thr Ser Ser Gly Asn Ser Ser Gln Glu Gly Pro Ser Asn Val
    1010                1015                1020
Pro Gly Ala Leu Asp Phe Glu His Ile Glu Glu Gln Ala Glu Gly Ile
1025                1030                1035                1040
Phe Gly Gly Ser Glu Glu Asn Thr Pro Leu Asp Leu Asp Asp His Gly
                1045                1050                1055
Gly Arg Thr Phe Leu Arg Val Leu Leu His Leu Thr Met His Asp Tyr
            1060                1065                1070
Pro Pro Leu Val Ser Gly Ala Leu Gln Leu Leu Phe Arg His Phe Ser
        1075                1080                1085
Gln Arg Gln Glu Val Leu Gln Ala Phe Lys Gln Val Gln Leu Leu Val
    1090                1095                1100
Thr Ser Gln Asp Val Asp Asn Tyr Lys Gln Ile Lys Gln Asp Leu Asp
1105                1110                1115                1120
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Gln Leu Arg Ser Ile Val Glu Lys Ser Glu Leu Trp Val Tyr Lys Gly
                1125                1130                1135
Gln Gly Pro Asp Glu Pro Met Asp Gly Ala Ser Gly Glu Asn Glu His
            1140                1145                1150
Lys Lys Thr Glu Glu Gly Thr Ser Lys Pro Leu Lys His Glu Ser Thr
        1155                1160                1165
Ser Ser Tyr Asn Tyr Arg Val Val Lys Glu Ile Leu Ile Arg Leu Ser
    1170                1175                1180
Lys Leu Cys Val Gln Glu Ser Ala Ser Val Arg Lys Ser Arg Lys Gln
1185                1190                1195                1200
Gln Gln Arg Leu Leu Arg Asn Met Gly Ala His Ala Val Val Leu Glu
                1205                1210                1215
Leu Leu Gln Ile Pro Tyr Glu Lys Ala Glu Asp Thr Lys Met Gln Glu
            1220                1225                1230
Ile Met Arg Leu Ala His Glu Phe Leu Gln Asn Phe Cys Ala Gly Asn
        1235                1240                1245
Gln Gln Asn Gln Ala Leu Leu His Lys His Ile Asn Leu Phe Leu Asn
    1250                1255                1260
Pro Gly Ile Leu Glu Ala Val Thr Met Gln His Ile Phe Met Asn Asn
1265                1270                1275                1280
Phe Gln Leu Cys Ser Glu Ile Asn Glu Arg Val Val Gln His Phe Val
                1285                1290                1295
His Cys Ile Glu Thr His Gly Arg Asn Val Gln Tyr Ile Lys Phe Leu
            1300                1305                1310
Gln Thr Ile Val Lys Ala Glu Gly Lys Phe Ile Lys Lys Cys Gln Asp
        1315                1320                1325
Met Val Met Ala Glu Leu Val Asn Ser Gly Glu Asp Val Leu Val Phe
    1330                1335                1340
Tyr Asn Asp Arg Ala Ser Phe Gln Thr Leu Ile Gln Met Met Arg Ser
1345                1350                1355                1360
Glu Arg Asp Arg Met Asp Glu Asn Ser Pro Leu Phe Met Tyr His Ile
                1365                1370                1375
His Leu Val Glu Leu Leu Ala Val Cys Thr Glu Gly Lys Asn Val Tyr
            1380                1385                1390
Thr Glu Ile Lys Cys Asn Ser Leu Leu Pro Leu Asp Asp Ile Val Arg
        1395                1400                1405
Val Val Thr His Glu Asp Cys Ile Pro Glu Val Lys Ile Ala Tyr Ile
    1410                1415                1420
Asn Phe Leu Asn His Cys Tyr Val Asp Thr Glu Val Glu Met Lys Glu
1425                1430                1435                1440
Ile Tyr Thr Ser Asn His Met Trp Lys Leu Phe Glu Asn Phe Leu Val
                1445                1450                1455
Asp Ile Cys Arg Ala Cys Asn Asn Thr Ser Asp Arg Lys His Ala Asp
            1460                1465                1470
Ser Val Leu Glu Lys Tyr Val Thr Glu Ile Val Met Ser Ile Val Thr
        1475                1480                1485
Thr Phe Phe Ser Ser Pro Phe Ser Asp Gln Ser Thr Thr Leu Gln Thr
    1490                1495                1500
Arg Gln Pro Val Phe Val Gln Leu Leu Gln Gly Val Phe Arg Val Tyr
1505                1510                1515                1520
His Cys Asn Trp Leu Met Pro Ser Gln Lys Ala Ser Val Glu Ser Cys
                1525                1530                1535
Ile Arg Val Leu Ser Asp Val Ala Lys Ser Arg Ala Ile Ala Ile Pro
            1540                1545                1550
Val Asp Leu Asp Ser Gln Val Asn Asn Leu Phe Leu Lys Ser His Asn
        1555                1560                1565
Ile Val Gln Lys Thr Ala Met Asn Trp Arg Leu Ser Ala Arg Asn Ala
    1570                1575                1580
Ala Arg Arg Asp Ser Val Leu Ala Ala Ser Arg Asp Tyr Arg Asn Ile
1585                1590                1595                1600
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Ile Glu Arg Leu Gln Asp Ile Val Ser Ala Leu Glu Asp Arg Leu Arg
1605 1610 1615
Pro Leu Val Gln Ala Glu Leu Ser Val Leu Val Asp Val Leu His Arg
1620 1625 1630
Pro Glu Leu Leu Phe Pro Glu Asn Thr Asp Ala Arg Arg Lys Cys Glu
1635 1640 1645
Ser Gly Gly Phe Ile Cys Lys Leu Ile Lys His Thr Lys Gln Leu Leu
1650 1655 1660
Glu Glu Asn Glu Glu Lys Leu Cys Ile Lys Val Leu Gln Thr Leu Arg
1665 1670 1675 1680
Glu Met Met Thr Lys Asp Arg Gly Tyr Gly Glu Lys Gln Ile Ser Ile
1685 1690 1695
Asp Glu Leu Glu Asn Ala Glu Leu Pro Gln Pro Pro Glu Ala Glu Asn
1700 1705 1710
Ser Thr Glu Glu Leu Glu Pro Ser Pro Pro Leu Arg Gln Leu Glu Asp
1715 1720 1725
His Lys Arg Gly Glu Ala Leu Arg Gln Ile Leu Val Asn Arg Tyr Tyr
1730 1735 1740
Gly Asn Ile Arg Pro Ser Gly Arg Arg Glu Asp Leu Thr Ser Phe Gly
1745 1750 1755 1760
Asn Gly Pro Leu Ser Pro Gly Gly Pro Ser Lys Pro Gly Gly Gly Gly
1765 1770 1775
Gly Gly Pro Gly Ser Gly Ser Thr Ser Arg Gly Glu Met Ser Leu Ala
1780 1785 1790
Glu Val Gln Cys His Leu Asp Lys Glu Gly Ala Ser Asn Leu Val Ile
1795 1800 1805
Asp Leu Ile Met Asn Ala Ser Ser Asp Arg Val Phe His Glu Ser Ile
1810 1815 1820
Leu Leu Ala Ile Ala Leu Leu Glu Gly Gly Asn Thr Thr Ile Gln His
1825 1830 1835 1840
Ser Phe Phe Cys Arg Leu Thr Glu Asp Lys Lys Ser Glu Lys Phe Phe
1845 1850 1855
Lys Val Phe Tyr Asp Arg Met Lys Val Ala Gln Gln Glu Ile Lys Ala
1860 1865 1870
Thr Val Thr Val Asn Thr Ser Asp Leu Gly Asn Lys Lys Lys Asp Asp
1875 1880 1885
Glu Val Asp Arg Asp Ala Pro Ser Arg Lys Lys Ala Lys Glu Pro Thr
1890 1895 1900
Thr Gln Ile Thr Glu Glu Val Arg Asp Gln Leu Leu Glu Ala Ser Ala
1905 1910 1915 1920
Ala Thr Arg Lys Ala Phe Thr Thr Phe Arg Arg Glu Ala Asp Pro Asp
1925 1930 1935
Asp His Tyr Gln Ser Gly Glu Gly Thr Gln Ala Thr Thr Asp Lys Ala
1940 1945 1950
Lys Asp Asp Leu Glu Met Ser Ala Val Ile Thr Ile Met Gln Pro Ile
1955 1960 1965
Leu Arg Phe Leu Gln Leu Leu Cys Glu Asn His Asn Arg Asp Leu Gln
1970 1975 1980
Asn Phe Leu Arg Cys Gln Asn Asn Lys Thr Asn Tyr Asn Leu Val Cys
1985 1990 1995 2000
Glu Thr Leu Gln Phe Leu Asp Cys Ile Cys Gly Ser Thr Thr Gly Gly
2005 2010 2015
Leu Gly Leu Leu Gly Leu Tyr Ile Asn Glu Lys Asn Val Ala Leu Ile
2020 2025 2030
Asn Gln Thr Leu Glu Ser Leu Thr Glu Tyr Cys Gln Gly Pro Cys His
2035 2040 2045
Glu Asn Gln Asn Cys Ile Ala Thr His Glu Ser Asn Gly Ile Asp Ile
2050 2055 2060
Ile Thr Ala Leu Ile Leu Asn Asp Ile Asn Pro Leu Gly Lys Lys Arg
2065 2070 2075 2080

Met Asp Leu Val Leu Glu Leu Lys Asn Asn Ala Ser Lys Leu Leu Leu
2085 2090 2095
Ala Ile Met Glu Ser Arg His Asp Ser Glu Asn Ala Glu Arg Ile Leu
2100 2105 2110
Tyr Asn Met Arg Pro Lys Glu Leu Val Glu Val Ile Lys Lys Ala Tyr
2115 2120 2125
Met Gln Gly Glu Val Glu Phe Glu Asp Gly Glu Asn Gly Glu Asp Gly
2130 2135 2140
Ala Ala Ser Pro Arg Asn Val Gly His Asn Ile Tyr Ile Leu Ala His
2145 2150 2155 2160
Gln Leu Ala Arg His Asn Lys Glu Leu Gln Thr Met Leu Lys Pro Gly
2165 2170 2175
Gly Gln Val Asp Gly Asp Glu Ala Leu Glu Phe Tyr Ala Lys His Thr
2180 2185 2190
Ala Gln Ile Glu Ile Val Arg Leu Asp Arg Thr Met Glu Gln Ile Val
2195 2200 2205
Phe Pro Val Pro Ser Ile Cys Glu Phe Leu Thr Lys Glu Ser Lys Leu
2210 2215 2220
Arg Ile Tyr Tyr Thr Thr Glu Arg Asp Glu Gln Gly Ser Lys Ile Asn
2225 2230 2235 2240
Asp Phe Phe Leu Arg Ser Glu Asp Leu Phe Asn Glu Met Asn Trp Gln
2245 2250 2255
Lys Lys Leu Arg Ala Gln Pro Val Leu Tyr Trp Cys Ala Arg Asn Met
2260 2265 2270
Ser Phe Trp Ser Ser Ile Ser Phe Asn Leu Ala Val Leu Met Asn Leu
2275 2280 2285
Leu Val Ala Phe Phe Tyr Pro Phe Lys Gly Val Arg Gly Gly Thr Leu
2290 2295 2300
Glu Pro His Trp Ser Gly Leu Leu Trp Thr Ala Met Leu Ile Ser Leu
2305 2310 2315 2320
Ala Ile Val Ile Ala Leu Pro Lys Pro His Gly Ile Arg Ala Leu Ile
2325 2330 2335
Ala Ser Thr Ile Leu Arg Leu Ile Phe Ser Val Gly Leu Gln Pro Thr
2340 2345 2350
Leu Phe Leu Leu Gly Ala Phe Asn Val Cys Asn Lys Ile Ile Phe Leu
2355 2360 2365
Met Ser Phe Val Gly Asn Cys Gly Thr Phe Thr Arg Gly Tyr Arg Ala
2370 2375 2380
Met Val Leu Asp Val Glu Phe Leu Tyr His Leu Leu Tyr Leu Leu Ile
2385 2390 2395 2400
Cys Ala Met Gly Leu Phe Val His Glu Phe Phe Tyr Ser Leu Leu Leu
2405 2410 2415
Phe Asp Leu Val Tyr Arg Glu Glu Thr Leu Leu Asn Val Ile Lys Ser
2420 2425 2430
Val Thr Arg Asn Gly Arg Pro Ile Ile Leu Thr Ala Ala Leu Ala Leu
2435 2440 2445
Ile Leu Val Tyr Leu Phe Ser Ile Val Gly Tyr Leu Phe Phe Lys Asp
2450 2455 2460
Asp Phe Ile Leu Glu Val Asp Arg Leu Pro Asn Glu Thr Ala Gly Pro
2465 2470 2475 2480
Glu Thr Gly Glu Ser Leu Ala Asn Asp Phe Leu Tyr Ser Asp Val Cys
2485 2490 2495
Arg Val Glu Thr Gly Glu Asn Cys Thr Ser Pro Ala Pro Lys Glu Glu
2500 2505 2510
Leu Leu Pro Val Glu Glu Thr Glu Gln Asp Lys Glu His Thr Cys Glu
2515 2520 2525
Thr Leu Leu Met Cys Ile Val Thr Val Leu Ser His Gly Leu Arg Ser
2530 2535 2540
Gly Gly Gly Val Gly Asp Val Leu Arg Lys Pro Ser Lys Glu Glu Pro
2545 2550 2555 2560

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Leu Phe Ala Ala Arg Val Ile Tyr Asp Leu Leu Phe Phe Phe Met Val
                2565                2570                2575
Ile Ile Ile Val Leu Asn Leu Ile Phe Gly Val Ile Ile Asp Thr Phe
            2580                2585                2590
Ala Asp Leu Arg Ser Glu Lys Gln Lys Lys Glu Glu Ile Leu Lys Thr
        2595                2600                2605
Thr Cys Phe Ile Cys Gly Leu Glu Arg Asp Lys Phe Asp Asn Lys Thr
    2610                2615                2620
Val Thr Phe Glu Glu His Ile Lys Glu Glu His Asn Met Trp His Tyr
2625                2630                2635                2640
Leu Cys Phe Ile Val Leu Val Lys Val Lys Asp Ser Thr Glu Tyr Thr
                2645                2650                2655
Gly Pro Glu Ser Tyr Val Ala Glu Met Ile Arg Glu Arg Asn Leu Asp
            2660                2665                2670
Trp Phe Pro Arg Met Arg Ala Met Ser Leu Val Ser Ser Asp Ser Glu
        2675                2680                2685
Gly Glu Gln Asn Glu Leu Arg Asn Leu Gln Glu Lys Leu Glu Ser Thr
    2690                2695                2700
Met Lys Leu Val Thr Asn Leu Ser Gly Gln Leu Ser Glu Leu Lys Asp
2705                2710                2715                2720
Gln Met Thr Glu Gln Arg Lys Gln Lys Gln Arg Ile Gly Leu Leu Gly
                2725                2730                2735
His Pro Pro His Met Asn Val Asn Pro Gln Gln Pro Ala
            2740                2745


<210> 9
<211> 2710
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/note =
      synthetic construct

<400> 9
Met Ser Asp Lys Met Ser Ser Phe Leu His Ile Gly Asp Ile Cys Ser
 1                5                  10                  15
Leu Tyr Ala Glu Gly Ser Thr Asn Gly Phe Ile Ser Thr Leu Gly Leu
            20                  25                  30
Val Asp Asp Arg Cys Val Val Gln Pro Glu Ala Gly Asp Leu Asn Asn
        35                  40                  45
Pro Pro Lys Lys Phe Arg Asp Cys Leu Phe Lys Leu Cys Pro Met Asn
    50                  55                  60
Arg Tyr Ser Ala Gln Lys Gln Phe Trp Lys Ala Ala Lys Pro Gly Ala
65                  70                  75                  80
Asn Ser Thr Thr Asp Ala Val Leu Leu Asn Lys Leu His His Ala Ala
                85                  90                  95
Asp Leu Glu Lys Lys Gln Asn Glu Thr Glu Asn Arg Lys Leu Leu Gly
            100                 105                 110
Thr Val Ile Gln Tyr Gly Asn Val Ile Gln Leu Leu His Leu Lys Ser
        115                 120                 125
Asn Lys Tyr Leu Thr Val Asn Lys Arg Leu Pro Ala Leu Leu Glu Lys
    130                 135                 140
Asn Ala Met Arg Val Thr Leu Asp Glu Ala Gly Asn Glu Gly Ser Trp
145                 150                 155                 160
Phe Tyr Ile Gln Pro Phe Tyr Lys Leu Arg Ser Ile Gly Asp Ser Val
                165                 170                 175
Val Ile Gly Asp Lys Val Val Leu Asn Pro Val Asn Ala Gly Gln Pro
            180                 185                 190
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```
Leu His Ala Ser Ser His Gln Leu Val Asp Asn Pro Gly Cys Asn Glu
        195                 200                 205
Val Asn Ser Val Asn Cys Asn Thr Ser Trp Lys Ile Val Leu Phe Met
    210                 215                 220
Lys Trp Ser Asp Asn Lys Asp Asp Ile Leu Lys Gly Gly Asp Val Val
225                 230                 235                 240
Arg Leu Phe His Ala Glu Gln Glu Lys Phe Leu Thr Cys Asp Glu His
                245                 250                 255
Arg Lys Lys Gln His Val Phe Leu Arg Thr Thr Gly Arg Gln Ser Ala
            260                 265                 270
Thr Ser Ala Thr Ser Ser Lys Ala Leu Trp Glu Val Glu Val Val Gln
        275                 280                 285
His Asp Pro Cys Arg Gly Gly Ala Gly Tyr Trp Asn Ser Leu Phe Arg
    290                 295                 300
Phe Lys His Leu Ala Thr Gly His Tyr Leu Ala Ala Glu Val Asp Pro
305                 310                 315                 320
Asp Phe Glu Glu Glu Cys Leu Glu Phe Gln Pro Ser Val Asp Pro Asp
                325                 330                 335
Gln Asp Ala Ser Arg Ser Arg Leu Arg Asn Ala Gln Glu Lys Met Val
            340                 345                 350
Tyr Ser Leu Val Ser Val Pro Glu Gly Asn Asp Ile Ser Ser Ile Phe
        355                 360                 365
Glu Leu Asp Pro Thr Thr Leu Arg Gly Gly Asp Ser Leu Val Pro Arg
    370                 375                 380
Asn Ser Tyr Val Arg Leu Arg His Leu Cys Thr Asn Thr Trp Val His
385                 390                 395                 400
Ser Thr Asn Ile Pro Ile Asp Lys Glu Glu Glu Lys Pro Val Met Leu
                405                 410                 415
Lys Ile Gly Thr Ser Pro Leu Lys Glu Asp Lys Glu Ala Phe Ala Ile
            420                 425                 430
Val Pro Val Ser Pro Ala Glu Val Arg Asp Leu Asp Phe Ala Asn Asp
        435                 440                 445
Ala Ser Lys Val Leu Gly Ser Ile Ala Gly Lys Leu Glu Lys Gly Thr
    450                 455                 460
Ile Thr Gln Asn Glu Arg Arg Ser Val Thr Lys Leu Leu Glu Asp Leu
465                 470                 475                 480
Val Tyr Phe Val Thr Gly Gly Thr Asn Ser Gly Gln Asp Val Leu Glu
                485                 490                 495
Val Val Phe Ser Lys Pro Asn Arg Glu Arg Gln Lys Leu Met Arg Glu
            500                 505                 510
Gln Asn Ile Leu Lys Gln Ile Phe Lys Leu Leu Gln Ala Pro Phe Thr
        515                 520                 525
Asp Cys Gly Asp Gly Pro Met Leu Arg Leu Glu Glu Leu Gly Asp Gln
    530                 535                 540
Arg His Ala Pro Phe Arg His Ile Cys Arg Leu Cys Tyr Arg Val Leu
545                 550                 555                 560
Arg His Ser Gln Gln Asp Tyr Arg Lys Asn Gln Glu Tyr Ile Ala Lys
                565                 570                 575
Gln Phe Gly Phe Met Gln Lys Gln Ile Gly Tyr Asp Val Leu Ala Glu
            580                 585                 590
Asp Thr Ile Thr Ala Leu Leu His Asn Asn Arg Lys Leu Leu Glu Lys
        595                 600                 605
His Ile Thr Ala Ala Glu Ile Asp Thr Phe Val Ser Leu Val Arg Lys
    610                 615                 620
Asn Arg Glu Pro Arg Phe Leu Asp Tyr Leu Ser Asp Leu Cys Val Ser
625                 630                 635                 640
Met Asn Lys Ser Ile Pro Val Thr Gln Glu Leu Ile Cys Lys Ala Val
                645                 650                 655
Leu Asn Pro Thr Asn Ala Asp Ile Leu Ile Glu Thr Lys Leu Val Leu
            660                 665                 670
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Ser Arg Phe Glu Phe Glu Gly Val Ser Thr Gly Glu Asn Ala Leu Glu
        675                 680                 685
Ala Gly Glu Asp Glu Glu Glu Val Trp Leu Phe Trp Arg Asp Ser Asn
    690                 695                 700
Lys Glu Ile Arg Ser Lys Ser Val Arg Glu Leu Ala Gln Asp Ala Lys
705                 710                 715                 720
Glu Gly Gln Lys Glu Asp Arg Asp Val Leu Ser Tyr Tyr Arg Tyr Gln
                725                 730                 735
Leu Asn Leu Phe Ala Arg Met Cys Leu Asp Arg Gln Tyr Leu Ala Ile
            740                 745                 750
Asn Glu Ile Ser Gly Gln Leu Asp Val Asp Leu Ile Leu Arg Cys Met
        755                 760                 765
Ser Asp Glu Asn Leu Pro Tyr Asp Leu Arg Ala Ser Phe Cys Arg Leu
    770                 775                 780
Met Leu His Met His Val Asp Arg Asp Pro Gln Glu Gln Val Thr Pro
785                 790                 795                 800
Val Lys Tyr Ala Arg Leu Trp Ser Glu Ile Pro Ser Glu Ile Ala Ile
                805                 810                 815
Asp Asp Tyr Asp Ser Ser Gly Ala Ser Lys Asp Glu Ile Lys Glu Arg
            820                 825                 830
Phe Ala Gln Thr Met Glu Phe Val Glu Glu Tyr Leu Arg Asp Val Val
        835                 840                 845
Cys Gln Arg Phe Pro Phe Ser Asp Lys Glu Lys Asn Lys Leu Thr Phe
    850                 855                 860
Glu Val Val Asn Leu Ala Arg Asn Leu Ile Tyr Phe Gly Phe Tyr Asn
865                 870                 875                 880
Phe Ser Asp Leu Leu Arg Leu Thr Lys Ile Leu Leu Ala Ile Leu Asp
                885                 890                 895
Cys Val His Val Thr Thr Ile Phe Pro Ile Ser Lys Met Thr Lys Gly
            900                 905                 910
Glu Glu Asn Lys Gly Ser Asn Val Met Arg Ser Ile His Gly Val Gly
        915                 920                 925
Glu Leu Met Thr Gln Val Val Leu Arg Gly Gly Gly Phe Leu Pro Met
    930                 935                 940
Thr Pro Met Ala Ala Ala Pro Glu Gly Asn Val Lys Gln Ala Glu Pro
945                 950                 955                 960
Glu Lys Glu Asp Ile Met Val Met Asp Thr Lys Leu Lys Ile Ile Glu
                965                 970                 975
Ile Leu Gln Phe Ile Leu Asn Val Arg Leu Asp Tyr Arg Ile Ser Cys
            980                 985                 990
Leu Leu Cys Ile Phe Lys Arg Glu Phe Asp Glu Ser Asn Ser Gln Ser
        995                 1000                1005
Ser Glu Thr Ser Ser Gly Asn Ser Ser Gln Glu Gly Pro Ser Asn Val
    1010                1015                1020
Pro Gly Ala Leu Asp Phe Glu His Ile Glu Glu Gln Ala Glu Gly Ile
1025                1030                1035                1040
Phe Gly Gly Ser Glu Glu Asn Thr Pro Leu Asp Leu Asp Asp His Gly
                1045                1050                1055
Gly Arg Thr Phe Leu Arg Val Leu Leu His Leu Thr Met His Asp Tyr
            1060                1065                1070
Pro Pro Leu Val Ser Gly Ala Leu Gln Leu Leu Phe Arg His Phe Ser
        1075                1080                1085
Gln Arg Gln Glu Val Leu Gln Ala Phe Lys Gln Val Gln Leu Leu Val
    1090                1095                1100
Thr Ser Gln Asp Val Asp Asn Tyr Lys Gln Ile Lys Gln Asp Leu Asp
1105                1110                1115                1120
Gln Leu Arg Ser Ile Val Glu Lys Ser Glu Leu Trp Val Tyr Lys Gly
                1125                1130                1135
Gln Gly Pro Asp Glu Pro Met Asp Gly Ala Ser Gly Glu Asn Glu His
            1140                1145                1150
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Lys Lys Thr Glu Glu Gly Thr Ser Lys Pro Leu Lys His Glu Ser Thr
        1155                1160                1165
Ser Ser Tyr Asn Tyr Arg Val Val Lys Glu Ile Leu Ile Arg Leu Ser
    1170                1175                1180
Lys Leu Cys Val Gln Glu Ser Ala Ser Val Arg Lys Ser Arg Lys Gln
1185                1190                1195                1200
Gln Gln Arg Leu Leu Arg Asn Met Gly Ala His Ala Val Val Leu Glu
                1205                1210                1215
Leu Leu Gln Ile Pro Tyr Glu Lys Ala Glu Asp Thr Lys Met Gln Glu
            1220                1225                1230
Ile Met Arg Leu Ala His Glu Phe Leu Gln Asn Phe Cys Ala Gly Asn
        1235                1240                1245
Gln Gln Asn Gln Ala Leu Leu His Lys His Ile Asn Leu Phe Leu Asn
    1250                1255                1260
Pro Gly Ile Leu Glu Ala Val Thr Met Gln His Ile Phe Met Asn Asn
1265                1270                1275                1280
Phe Gln Leu Cys Ser Glu Ile Asn Glu Arg Val Val Gln His Phe Val
                1285                1290                1295
His Cys Ile Glu Thr His Gly Arg Asn Val Gln Tyr Ile Lys Phe Leu
            1300                1305                1310
Gln Thr Ile Val Lys Ala Glu Gly Lys Phe Ile Lys Lys Cys Gln Asp
        1315                1320                1325
Met Val Met Ala Glu Leu Val Asn Ser Gly Glu Asp Val Leu Val Phe
    1330                1335                1340
Tyr Asn Asp Arg Ala Ser Phe Gln Thr Leu Ile Gln Met Met Arg Ser
1345                1350                1355                1360
Glu Arg Asp Arg Met Asp Glu Asn Ser Pro Leu Phe Met Tyr His Ile
                1365                1370                1375
His Leu Val Glu Leu Leu Ala Val Cys Thr Glu Gly Lys Asn Val Tyr
            1380                1385                1390
Thr Glu Ile Lys Cys Asn Ser Leu Leu Pro Leu Asp Asp Ile Val Arg
        1395                1400                1405
Val Val Thr His Glu Asp Cys Ile Pro Glu Val Lys Ile Ala Tyr Ile
    1410                1415                1420
Asn Phe Leu Asn His Cys Tyr Val Asp Thr Glu Val Glu Met Lys Glu
1425                1430                1435                1440
Ile Tyr Thr Ser Asn His Met Trp Lys Leu Phe Glu Asn Phe Leu Val
                1445                1450                1455
Asp Ile Cys Arg Ala Cys Asn Asn Thr Ser Asp Arg Lys His Ala Asp
            1460                1465                1470
Ser Val Leu Glu Lys Tyr Val Thr Glu Ile Val Met Ser Ile Val Thr
        1475                1480                1485
Thr Phe Phe Ser Ser Pro Phe Ser Asp Gln Ser Thr Thr Leu Gln Thr
    1490                1495                1500
Arg Gln Pro Val Phe Val Gln Leu Leu Gln Gly Val Phe Arg Val Tyr
1505                1510                1515                1520
His Cys Asn Trp Leu Met Pro Ser Gln Lys Ala Ser Val Glu Ser Cys
                1525                1530                1535
Ile Arg Val Leu Ser Asp Val Ala Lys Ser Arg Ala Ile Ala Ile Pro
            1540                1545                1550
Val Asp Leu Asp Ser Gln Val Asn Asn Leu Phe Leu Lys Ser His Asn
        1555                1560                1565
Ile Val Gln Lys Thr Ala Met Asn Trp Arg Leu Ser Ala Arg Asn Ala
    1570                1575                1580
Ala Arg Arg Asp Glu Val Leu Ala Ala Ser Arg Asp Tyr Arg Asn Ile
1585                1590                1595                1600
Ile Glu Arg Leu Gln Asp Ile Val Ser Ala Leu Glu Asp Arg Leu Arg
                1605                1610                1615
Pro Leu Val Gln Ala Glu Leu Ser Val Leu Val Asp Val Leu His Arg
            1620                1625                1630
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Pro Glu Leu Leu Phe Pro Glu Asn Thr Asp Ala Arg Arg Lys Cys Glu
        1635                1640                1645
Ser Gly Gly Phe Ile Cys Lys Leu Ile Lys His Thr Lys Gln Leu Leu
    1650                1655                1660
Glu Glu Asn Glu Glu Lys Leu Cys Ile Lys Val Leu Gln Thr Leu Arg
1665                1670                1675                1680
Glu Met Met Thr Lys Asp Arg Gly Tyr Gly Glu Lys Gly Glu Ala Leu
                1685                1690                1695
Arg Gln Ile Leu Val Asn Arg Tyr Tyr Gly Asn Ile Arg Pro Ser Gly
            1700                1705                1710
Arg Arg Glu Glu Leu Thr Ser Phe Gly Asn Gly Pro Leu Ser Pro Gly
        1715                1720                1725
Gly Pro Ser Lys Pro Gly Gly Gly Gly Gly Gly Pro Gly Ser Gly Ser
    1730                1735                1740
Thr Ser Arg Gly Glu Met Ser Leu Ala Glu Val Gln Cys His Leu Asp
1745                1750                1755                1760
Lys Glu Gly Ala Ser Asn Leu Val Ile Asp Leu Ile Met Asn Ala Ser
                1765                1770                1775
Ser Asp Arg Val Phe His Glu Ser Ile Leu Leu Ala Ile Ala Leu Leu
            1780                1785                1790
Glu Gly Gly Asn Thr Thr Ile Gln His Ser Phe Phe Cys Arg Leu Thr
        1795                1800                1805
Glu Asp Lys Lys Ser Glu Lys Phe Phe Lys Val Phe Tyr Asp Arg Met
    1810                1815                1820
Lys Val Ala Gln Gln Glu Ile Lys Ala Thr Val Thr Val Asn Thr Ser
1825                1830                1835                1840
Asp Leu Gly Asn Lys Lys Lys Asp Asp Glu Val Asp Arg Asp Ala Pro
                1845                1850                1855
Ser Arg Lys Lys Ala Lys Glu Pro Thr Thr Gln Ile Thr Glu Glu Val
            1860                1865                1870
Arg Asp Gln Leu Leu Glu Ala Ser Ala Ala Thr Arg Lys Ala Phe Thr
        1875                1880                1885
Thr Phe Arg Arg Glu Ala Asp Pro Asp Asp His Tyr Gln Ser Gly Glu
    1890                1895                1900
Gly Thr Gln Ala Thr Thr Asp Lys Ala Lys Asp Asp Leu Glu Met Ser
1905                1910                1915                1920
Ala Val Ile Thr Ile Met Gln Pro Ile Leu Arg Phe Leu Gln Leu Leu
                1925                1930                1935
Cys Glu Asn His Asn Arg Asp Leu Gln Asn Phe Leu Arg Cys Gln Asn
            1940                1945                1950
Asn Lys Thr Asn Tyr Asn Leu Val Cys Glu Thr Leu Gln Phe Leu Asp
        1955                1960                1965
Cys Ile Cys Gly Ser Thr Thr Gly Gly Leu Gly Leu Leu Gly Leu Tyr
    1970                1975                1980
Ile Asn Glu Lys Asn Val Ala Leu Ile Asn Gln Thr Leu Glu Ser Leu
1985                1990                1995                2000
Thr Glu Tyr Cys Gln Gly Pro Cys His Glu Asn Gln Asn Cys Ile Ala
                2005                2010                2015
Thr His Glu Ser Asn Gly Ile Asp Ile Ile Thr Ala Leu Ile Leu Asn
            2020                2025                2030
Asp Ile Asn Pro Leu Gly Lys Lys Arg Met Asp Leu Val Leu Glu Leu
        2035                2040                2045
Lys Asn Asn Ala Ser Lys Leu Leu Leu Ala Ile Met Glu Ser Arg His
    2050                2055                2060
Asp Ser Glu Asn Ala Glu Arg Ile Leu Tyr Asn Met Arg Pro Lys Glu
2065                2070                2075                2080
Leu Val Glu Val Ile Lys Lys Ala Tyr Met Gln Gly Glu Val Glu Phe
                2085                2090                2095
Glu Asp Gly Glu Asn Gly Glu Asp Gly Ala Ala Ser Pro Arg Asn Val
            2100                2105                2110
```

Gly His Asn Ile Tyr Ile Leu Ala His Gln Leu Ala Arg His Asn Lys
2115 2120 2125
Glu Leu Gln Thr Met Leu Lys Pro Gly Gly Gln Val Asp Gly Asp Glu
2130 2135 2140
Ala Leu Glu Phe Tyr Ala Lys His Thr Ala Gln Ile Glu Ile Val Arg
2145 2150 2155 2160
Leu Asp Arg Thr Met Glu Gln Ile Val Phe Pro Val Pro Ser Ile Cys
2165 2170 2175
Glu Phe Leu Thr Lys Glu Ser Lys Leu Arg Ile Tyr Tyr Thr Thr Glu
2180 2185 2190
Arg Asp Glu Gln Gly Ser Lys Ile Asn Asp Phe Phe Leu Arg Ser Glu
2195 2200 2205
Asp Leu Phe Asn Glu Met Asn Trp Gln Lys Lys Leu Arg Ala Gln Pro
2210 2215 2220
Val Leu Tyr Trp Cys Ala Arg Asn Met Ser Phe Trp Ser Ser Ile Ser
2225 2230 2235 2240
Phe Asn Leu Ala Val Leu Met Asn Leu Leu Val Ala Phe Phe Tyr Pro
2245 2250 2255
Phe Lys Gly Val Arg Gly Gly Thr Leu Glu Pro His Trp Ser Gly Leu
2260 2265 2270
Leu Trp Thr Ala Met Leu Ile Ser Leu Ala Ile Val Ile Ala Leu Pro
2275 2280 2285
Lys Pro His Gly Ile Arg Ala Leu Ile Ala Ser Thr Ile Leu Arg Leu
2290 2295 2300
Ile Phe Ser Val Gly Leu Gln Pro Thr Leu Phe Leu Leu Gly Ala Phe
2305 2310 2315 2320
Asn Val Cys Asn Lys Ile Ile Phe Leu Met Ser Phe Val Gly Asn Cys
2325 2330 2335
Gly Thr Phe Thr Arg Gly Tyr Arg Ala Met Val Leu Asp Val Glu Phe
2340 2345 2350
Leu Tyr His Leu Leu Tyr Leu Leu Ile Cys Ala Met Gly Leu Phe Val
2355 2360 2365
His Glu Phe Phe Tyr Ser Leu Leu Leu Phe Asp Leu Val Tyr Arg Glu
2370 2375 2380
Glu Thr Leu Leu Asn Val Ile Lys Ser Val Thr Arg Asn Gly Arg Pro
2385 2390 2395 2400
Ile Ile Leu Thr Ala Ala Leu Ala Leu Ile Leu Val Tyr Leu Phe Ser
2405 2410 2415
Ile Val Gly Tyr Leu Phe Phe Lys Asp Asp Phe Ile Leu Glu Val Asp
2420 2425 2430
Arg Leu Pro Asn Glu Thr Ala Gly Pro Glu Thr Gly Glu Ser Leu Ala
2435 2440 2445
Asn Asp Phe Leu Tyr Ser Asp Val Cys Arg Val Glu Thr Gly Glu Asn
2450 2455 2460
Cys Thr Ser Pro Ala Pro Lys Glu Glu Leu Leu Pro Val Glu Glu Thr
2465 2470 2475 2480
Glu Gln Asp Lys Glu His Thr Cys Glu Thr Leu Leu Met Cys Ile Val
2485 2490 2495
Thr Val Leu Ser His Gly Leu Arg Ser Gly Gly Gly Val Gly Asp Val
2500 2505 2510
Leu Arg Lys Pro Ser Lys Glu Glu Pro Leu Phe Ala Ala Arg Val Ile
2515 2520 2525
Tyr Asp Leu Leu Phe Phe Phe Met Val Ile Ile Ile Val Leu Asn Leu
2530 2535 2540
Ile Phe Gly Val Ile Ile Asp Thr Phe Ala Asp Leu Arg Ser Glu Lys
2545 2550 2555 2560
Gln Lys Lys Glu Glu Ile Leu Lys Thr Thr Cys Phe Ile Cys Gly Leu
2565 2570 2575
Glu Arg Asp Lys Phe Asp Asn Lys Thr Val Thr Phe Glu Glu His Ile
2580 2585 2590

```
Lys Glu Glu His Asn Met Trp His Tyr Leu Cys Phe Ile Val Leu Val
        2595                2600                2605
Lys Val Lys Asp Ser Thr Glu Tyr Thr Gly Pro Glu Ser Tyr Val Ala
    2610                2615                2620
Glu Met Ile Arg Glu Arg Asn Leu Asp Trp Phe Pro Arg Met Arg Ala
2625                2630                2635                2640
Met Ser Leu Val Ser Ser Asp Ser Glu Gly Glu Gln Asn Glu Leu Arg
                2645                2650                2655
Asn Leu Gln Glu Lys Leu Glu Ser Thr Met Lys Leu Val Thr Asn Leu
            2660                2665                2670
Ser Gly Gln Leu Ser Glu Leu Lys Asp Gln Met Thr Glu Gln Arg Lys
        2675                2680                2685
Gln Lys Gln Arg Ile Gly Leu Leu Gly His Pro Pro His Met Asn Val
    2690                2695                2700
Asn Pro Gln Gln Pro Ala
2705                2710


<210> 10
<211> 2749
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/note =
      synthetic construct

<400> 10
Met Ser Asp Lys Met Ser Ser Phe Leu His Ile Gly Asp Ile Cys Ser
 1                5                  10                  15
Leu Tyr Ala Glu Gly Ser Thr Asn Gly Phe Ile Ser Thr Leu Gly Leu
            20                  25                  30
Val Asp Asp Arg Cys Val Val Gln Pro Glu Ala Gly Asp Leu Asn Asn
        35                  40                  45
Pro Pro Lys Lys Phe Arg Asp Cys Leu Phe Lys Leu Cys Pro Met Asn
    50                  55                  60
Arg Tyr Ser Ala Gln Lys Gln Phe Trp Lys Ala Ala Lys Pro Gly Ala
65                  70                  75                  80
Asn Ser Thr Thr Asp Ala Val Leu Leu Asn Lys Leu His His Ala Ala
                85                  90                  95
Asp Leu Glu Lys Lys Gln Asn Glu Thr Glu Asn Arg Lys Leu Leu Gly
            100                 105                 110
Thr Val Ile Gln Tyr Gly Asn Val Ile Gln Leu Leu His Leu Lys Ser
        115                 120                 125
Asn Lys Tyr Leu Thr Val Asn Lys Arg Leu Pro Ala Leu Leu Glu Lys
    130                 135                 140
Asn Ala Met Arg Val Thr Leu Asp Glu Ala Gly Asn Glu Gly Ser Trp
145                 150                 155                 160
Phe Tyr Ile Gln Pro Phe Tyr Lys Leu Arg Ser Ile Gly Asp Ser Val
                165                 170                 175
Val Ile Gly Asp Lys Val Val Leu Asn Pro Val Asn Ala Gly Gln Pro
            180                 185                 190
Leu His Ala Ser Ser His Gln Leu Val Asp Asn Pro Gly Cys Asn Glu
        195                 200                 205
Val Asn Ser Val Asn Cys Asn Thr Ser Trp Lys Ile Val Leu Phe Met
    210                 215                 220
Lys Trp Ser Asp Asn Lys Asp Asp Ile Leu Lys Gly Gly Asp Val Val
225                 230                 235                 240
Arg Leu Phe His Ala Glu Gln Glu Lys Phe Leu Thr Cys Asp Glu His
                245                 250                 255
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```
Arg Lys Lys Gln His Val Phe Leu Arg Thr Thr Gly Arg Gln Ser Ala
            260                 265                 270
Thr Ser Ala Thr Ser Ser Lys Ala Leu Trp Glu Val Glu Val Val Gln
        275                 280                 285
His Asp Pro Cys Arg Gly Gly Ala Gly Tyr Trp Asn Ser Leu Phe Arg
    290                 295                 300
Phe Lys His Leu Ala Thr Gly His Tyr Leu Ala Ala Glu Val Asp Pro
305                 310                 315                 320
Asp Phe Glu Glu Glu Cys Leu Glu Phe Gln Pro Ser Val Asp Pro Asp
                325                 330                 335
Gln Asp Ala Ser Arg Ser Arg Leu Arg Asn Ala Gln Glu Lys Met Val
            340                 345                 350
Tyr Ser Leu Val Ser Val Pro Glu Gly Asn Asp Ile Ser Ser Ile Phe
        355                 360                 365
Glu Leu Asp Pro Thr Thr Leu Arg Gly Gly Asp Ser Leu Val Pro Arg
    370                 375                 380
Asn Ser Tyr Val Arg Leu Arg His Leu Cys Thr Asn Thr Trp Val His
385                 390                 395                 400
Ser Thr Asn Ile Pro Ile Asp Lys Glu Glu Glu Lys Pro Val Met Leu
                405                 410                 415
Lys Ile Gly Thr Ser Pro Leu Lys Glu Asp Lys Glu Ala Phe Ala Ile
            420                 425                 430
Val Pro Val Ser Pro Ala Glu Val Arg Asp Leu Asp Phe Ala Asn Asp
        435                 440                 445
Ala Ser Lys Val Leu Gly Ser Ile Ala Gly Lys Leu Glu Lys Gly Thr
    450                 455                 460
Ile Thr Gln Asn Glu Arg Arg Ser Val Thr Lys Leu Leu Glu Asp Leu
465                 470                 475                 480
Val Tyr Phe Val Thr Gly Gly Thr Asn Ser Gly Gln Asp Val Leu Glu
                485                 490                 495
Val Val Phe Ser Lys Pro Asn Arg Glu Arg Gln Lys Leu Met Arg Glu
            500                 505                 510
Gln Asn Ile Leu Lys Gln Ile Phe Lys Leu Leu Gln Ala Pro Phe Thr
        515                 520                 525
Asp Cys Gly Asp Gly Pro Met Leu Arg Leu Glu Glu Leu Gly Asp Gln
    530                 535                 540
Arg His Ala Pro Phe Arg His Ile Cys Arg Leu Cys Tyr Arg Val Leu
545                 550                 555                 560
Arg His Ser Gln Gln Asp Tyr Arg Lys Asn Gln Glu Tyr Ile Ala Lys
                565                 570                 575
Gln Phe Gly Phe Met Gln Lys Gln Ile Gly Tyr Asp Val Leu Ala Glu
            580                 585                 590
Asp Thr Ile Thr Ala Leu Leu His Asn Asn Arg Lys Leu Leu Glu Lys
        595                 600                 605
His Ile Thr Ala Ala Glu Ile Asp Thr Phe Val Ser Leu Val Arg Lys
    610                 615                 620
Asn Arg Glu Pro Arg Phe Leu Asp Tyr Leu Ser Asp Leu Cys Val Ser
625                 630                 635                 640
Met Asn Lys Ser Ile Pro Val Thr Gln Glu Leu Ile Cys Lys Ala Val
                645                 650                 655
Leu Asn Pro Thr Asn Ala Asp Ile Leu Ile Glu Thr Lys Leu Val Leu
            660                 665                 670
Ser Arg Phe Glu Phe Glu Gly Val Ser Thr Gly Glu Asn Ala Leu Glu
        675                 680                 685
Ala Gly Glu Asp Glu Glu Glu Val Trp Leu Phe Trp Arg Asp Ser Asn
    690                 695                 700
Lys Glu Ile Arg Ser Lys Ser Val Arg Glu Leu Ala Gln Asp Ala Lys
705                 710                 715                 720
Glu Gly Gln Lys Glu Asp Arg Asp Val Leu Ser Tyr Tyr Arg Tyr Gln
                725                 730                 735
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Leu Asn Leu Phe Ala Arg Met Cys Leu Asp Arg Gln Tyr Leu Ala Ile
            740                 745                 750
Asn Glu Ile Ser Gly Gln Leu Asp Val Asp Leu Ile Leu Arg Cys Met
        755                 760                 765
Ser Asp Glu Asn Leu Pro Tyr Asp Leu Arg Ala Ser Phe Cys Arg Leu
    770                 775                 780
Met Leu His Met His Val Asp Arg Asp Pro Gln Glu Gln Val Thr Pro
785                 790                 795                 800
Val Lys Tyr Ala Arg Leu Trp Ser Glu Ile Pro Ser Glu Ile Ala Ile
                805                 810                 815
Asp Asp Tyr Asp Ser Ser Gly Ala Ser Lys Asp Glu Ile Lys Glu Arg
            820                 825                 830
Phe Ala Gln Thr Met Glu Phe Val Glu Glu Tyr Leu Arg Asp Val Val
        835                 840                 845
Cys Gln Arg Phe Pro Phe Ser Asp Lys Glu Lys Asn Lys Leu Thr Phe
    850                 855                 860
Glu Val Val Asn Leu Ala Arg Asn Leu Ile Tyr Phe Gly Phe Tyr Asn
865                 870                 875                 880
Phe Ser Asp Leu Leu Arg Leu Thr Lys Ile Leu Leu Ala Ile Leu Asp
                885                 890                 895
Cys Val His Val Thr Thr Ile Phe Pro Ile Ser Lys Met Thr Lys Gly
            900                 905                 910
Glu Glu Asn Lys Gly Ser Asn Val Met Arg Ser Ile His Gly Val Gly
        915                 920                 925
Glu Leu Met Thr Gln Val Val Leu Arg Gly Gly Gly Phe Leu Pro Met
    930                 935                 940
Thr Pro Met Ala Ala Ala Pro Glu Gly Asn Val Lys Gln Ala Glu Pro
945                 950                 955                 960
Glu Lys Glu Asp Ile Met Val Met Asp Thr Lys Leu Lys Ile Ile Glu
                965                 970                 975
Ile Leu Gln Phe Ile Leu Asn Val Arg Leu Asp Tyr Arg Ile Ser Cys
            980                 985                 990
Leu Leu Cys Ile Phe Lys Arg Glu Phe Asp Glu Ser Asn Ser Gln Ser
        995                 1000                1005
Ser Glu Thr Ser Ser Gly Asn Ser Ser Gln Glu Gly Pro Ser Asn Val
    1010                1015                1020
Pro Gly Ala Leu Asp Phe Glu His Ile Glu Glu Gln Ala Glu Gly Ile
1025                1030                1035                1040
Phe Gly Gly Ser Glu Glu Asn Thr Pro Leu Asp Leu Asp Asp His Gly
                1045                1050                1055
Gly Arg Thr Phe Leu Arg Val Leu Leu His Leu Thr Met His Asp Tyr
            1060                1065                1070
Pro Pro Leu Val Ser Gly Ala Leu Gln Leu Leu Phe Arg His Phe Ser
        1075                1080                1085
Gln Arg Gln Glu Val Leu Gln Ala Phe Lys Gln Val Gln Leu Leu Val
    1090                1095                1100
Thr Ser Gln Asp Val Asp Asn Tyr Lys Gln Ile Lys Gln Asp Leu Asp
1105                1110                1115                1120
Gln Leu Arg Ser Ile Val Glu Lys Ser Glu Leu Trp Val Tyr Lys Gly
                1125                1130                1135
Gln Gly Pro Asp Glu Pro Met Asp Gly Ala Ser Gly Glu Asn Glu His
            1140                1145                1150
Lys Lys Thr Glu Glu Gly Thr Ser Lys Pro Leu Lys His Glu Ser Thr
        1155                1160                1165
Ser Ser Tyr Asn Tyr Arg Val Val Lys Glu Ile Leu Ile Arg Leu Ser
    1170                1175                1180
Lys Leu Cys Val Gln Glu Ser Ala Ser Val Arg Lys Ser Arg Lys Gln
1185                1190                1195                1200
Gln Gln Arg Leu Leu Arg Asn Met Gly Ala His Ala Val Val Leu Glu
                1205                1210                1215
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Leu Leu Gln Ile Pro Tyr Glu Lys Ala Glu Asp Thr Lys Met Gln Glu
            1220                1225                1230
Ile Met Arg Leu Ala His Glu Phe Leu Gln Asn Phe Cys Ala Gly Asn
        1235                1240                1245
Gln Gln Asn Gln Ala Leu Leu His Lys His Ile Asn Leu Phe Leu Asn
    1250                1255                1260
Pro Gly Ile Leu Glu Ala Val Thr Met Gln His Ile Phe Met Asn Asn
1265                1270                1275                1280
Phe Gln Leu Cys Ser Glu Ile Asn Glu Arg Val Val Gln His Phe Val
                1285                1290                1295
His Cys Ile Glu Thr His Gly Arg Asn Val Gln Tyr Ile Lys Phe Leu
            1300                1305                1310
Gln Thr Ile Val Lys Ala Glu Gly Lys Phe Ile Lys Lys Cys Gln Asp
        1315                1320                1325
Met Val Met Ala Glu Leu Val Asn Ser Gly Glu Asp Val Leu Val Phe
    1330                1335                1340
Tyr Asn Asp Arg Ala Ser Phe Gln Thr Leu Ile Gln Met Met Arg Ser
1345                1350                1355                1360
Glu Arg Asp Arg Met Asp Glu Asn Ser Pro Leu Phe Met Tyr His Ile
                1365                1370                1375
His Leu Val Glu Leu Leu Ala Val Cys Thr Glu Gly Lys Asn Val Tyr
            1380                1385                1390
Thr Glu Ile Lys Cys Asn Ser Leu Leu Pro Leu Asp Asp Ile Val Arg
        1395                1400                1405
Val Val Thr His Glu Asp Cys Ile Pro Glu Val Lys Ile Ala Tyr Ile
    1410                1415                1420
Asn Phe Leu Asn His Cys Tyr Val Asp Thr Glu Val Glu Met Lys Glu
1425                1430                1435                1440
Ile Tyr Thr Ser Asn His Met Trp Lys Leu Phe Glu Asn Phe Leu Val
                1445                1450                1455
Asp Ile Cys Arg Ala Cys Asn Asn Thr Ser Asp Arg Lys His Ala Asp
            1460                1465                1470
Ser Val Leu Glu Lys Tyr Val Thr Glu Ile Val Met Ser Ile Val Thr
        1475                1480                1485
Thr Phe Phe Ser Ser Pro Phe Ser Asp Gln Ser Thr Thr Leu Gln Thr
    1490                1495                1500
Arg Gln Pro Val Phe Val Gln Leu Leu Gln Gly Val Phe Arg Val Tyr
1505                1510                1515                1520
His Cys Asn Trp Leu Met Pro Ser Gln Lys Ala Ser Val Glu Ser Cys
                1525                1530                1535
Ile Arg Val Leu Ser Asp Val Ala Lys Ser Arg Ala Ile Ala Ile Pro
            1540                1545                1550
Val Asp Leu Asp Ser Gln Val Asn Asn Leu Phe Leu Lys Ser His Asn
        1555                1560                1565
Ile Val Gln Lys Thr Ala Met Asn Trp Arg Leu Ser Ala Arg Asn Ala
    1570                1575                1580
Ala Arg Arg Asp Glu Val Leu Ala Ala Ser Arg Asp Tyr Arg Asn Ile
1585                1590                1595                1600
Ile Glu Arg Leu Gln Asp Ile Val Ser Ala Leu Glu Asp Arg Leu Arg
                1605                1610                1615
Pro Leu Val Gln Ala Glu Leu Ser Val Leu Val Asp Val Leu His Arg
            1620                1625                1630
Pro Glu Leu Leu Phe Pro Glu Asn Thr Asp Ala Arg Arg Lys Cys Glu
        1635                1640                1645
Ser Gly Gly Phe Ile Cys Lys Leu Ile Lys His Thr Lys Gln Leu Leu
    1650                1655                1660
Glu Glu Asn Glu Glu Lys Leu Cys Ile Lys Val Leu Gln Thr Leu Arg
1665                1670                1675                1680
Glu Met Met Thr Lys Asp Arg Gly Tyr Gly Glu Lys Gln Ile Ser Ile
                1685                1690                1695
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Asp Glu Leu Glu Asn Ala Glu Leu Pro Gln Pro Pro Glu Ala Glu Asn
            1700                1705                1710
Ser Thr Glu Glu Leu Glu Pro Ser Pro Pro Leu Arg Gln Leu Glu Asp
        1715                1720                1725
His Lys Arg Gly Glu Ala Leu Arg Gln Ile Leu Val Asn Arg Tyr Tyr
    1730                1735                1740
Gly Asn Ile Arg Pro Ser Gly Arg Arg Glu Glu Leu Thr Ser Phe Gly
1745                1750                1755                1760
Asn Gly Pro Leu Ser Pro Gly Gly Pro Ser Lys Pro Gly Gly Gly Gly
                1765                1770                1775
Gly Gly Pro Gly Ser Gly Ser Thr Ser Arg Gly Glu Met Ser Leu Ala
            1780                1785                1790
Glu Val Gln Cys His Leu Asp Lys Glu Gly Ala Ser Asn Leu Val Ile
        1795                1800                1805
Asp Leu Ile Met Asn Ala Ser Ser Asp Arg Val Phe His Glu Ser Ile
    1810                1815                1820
Leu Leu Ala Ile Ala Leu Leu Glu Gly Gly Asn Thr Thr Ile Gln His
1825                1830                1835                1840
Ser Phe Phe Cys Arg Leu Thr Glu Asp Lys Lys Ser Glu Lys Phe Phe
                1845                1850                1855
Lys Val Phe Tyr Asp Arg Met Lys Val Ala Gln Gln Glu Ile Lys Ala
            1860                1865                1870
Thr Val Thr Val Asn Thr Ser Asp Leu Gly Asn Lys Lys Lys Asp Asp
        1875                1880                1885
Glu Val Asp Arg Asp Ala Pro Ser Arg Lys Lys Ala Lys Glu Pro Thr
    1890                1895                1900
Thr Gln Ile Thr Glu Glu Val Arg Asp Gln Leu Leu Glu Ala Ser Ala
1905                1910                1915                1920
Ala Thr Arg Lys Ala Phe Thr Thr Phe Arg Arg Glu Ala Asp Pro Asp
                1925                1930                1935
Asp His Tyr Gln Ser Gly Glu Gly Thr Gln Ala Thr Thr Asp Lys Ala
            1940                1945                1950
Lys Asp Asp Leu Glu Met Ser Ala Val Ile Thr Ile Met Gln Pro Ile
        1955                1960                1965
Leu Arg Phe Leu Gln Leu Leu Cys Glu Asn His Asn Arg Asp Leu Gln
    1970                1975                1980
Asn Phe Leu Arg Cys Gln Asn Asn Lys Thr Asn Tyr Asn Leu Val Cys
1985                1990                1995                2000
Glu Thr Leu Gln Phe Leu Asp Cys Ile Cys Gly Ser Thr Thr Gly Gly
                2005                2010                2015
Leu Gly Leu Leu Gly Leu Tyr Ile Asn Glu Lys Asn Val Ala Leu Ile
            2020                2025                2030
Asn Gln Thr Leu Glu Ser Leu Thr Glu Tyr Cys Gln Gly Pro Cys His
        2035                2040                2045
Glu Asn Gln Asn Cys Ile Ala Thr His Glu Ser Asn Gly Ile Asp Ile
    2050                2055                2060
Ile Thr Ala Leu Ile Leu Asn Asp Ile Asn Pro Leu Gly Lys Lys Arg
2065                2070                2075                2080
Met Asp Leu Val Leu Glu Leu Lys Asn Asn Ala Ser Lys Leu Leu Leu
                2085                2090                2095
Ala Ile Met Glu Ser Arg His Asp Ser Glu Asn Ala Glu Arg Ile Leu
            2100                2105                2110
Tyr Asn Met Arg Pro Lys Glu Leu Val Glu Val Ile Lys Lys Ala Tyr
        2115                2120                2125
Met Gln Gly Glu Val Glu Phe Glu Asp Gly Glu Asn Gly Glu Asp Gly
    2130                2135                2140
Ala Ala Ser Pro Arg Asn Val Gly His Asn Ile Tyr Ile Leu Ala His
2145                2150                2155                2160
Gln Leu Ala Arg His Asn Lys Glu Leu Gln Thr Met Leu Lys Pro Gly
                2165                2170                2175
```

Gly Gln Val Asp Gly Asp Glu Ala Leu Glu Phe Tyr Ala Lys His Thr
2180 2185 2190
Ala Gln Ile Glu Ile Val Arg Leu Asp Arg Thr Met Glu Gln Ile Val
2195 2200 2205
Phe Pro Val Pro Ser Ile Cys Glu Phe Leu Thr Lys Glu Ser Lys Leu
2210 2215 2220
Arg Ile Tyr Tyr Thr Thr Glu Arg Asp Glu Gln Gly Ser Lys Ile Asn
2225 2230 2235 2240
Asp Phe Phe Leu Arg Ser Glu Asp Leu Phe Asn Glu Met Asn Trp Gln
2245 2250 2255
Lys Lys Leu Arg Ala Gln Pro Val Leu Tyr Trp Cys Ala Arg Asn Met
2260 2265 2270
Ser Phe Trp Ser Ser Ile Ser Phe Asn Leu Ala Val Leu Met Asn Leu
2275 2280 2285
Leu Val Ala Phe Phe Tyr Pro Phe Lys Gly Val Arg Gly Gly Thr Leu
2290 2295 2300
Glu Pro His Trp Ser Gly Leu Leu Trp Thr Ala Met Leu Ile Ser Leu
2305 2310 2315 2320
Ala Ile Val Ile Ala Leu Pro Lys Pro His Gly Ile Arg Ala Leu Ile
2325 2330 2335
Ala Ser Thr Ile Leu Arg Leu Ile Phe Ser Val Gly Leu Gln Pro Thr
2340 2345 2350
Leu Phe Leu Leu Gly Ala Phe Asn Val Cys Asn Lys Ile Ile Phe Leu
2355 2360 2365
Met Ser Phe Val Gly Asn Cys Gly Thr Phe Thr Arg Gly Tyr Arg Ala
2370 2375 2380
Met Val Leu Asp Val Glu Phe Leu Tyr His Leu Leu Tyr Leu Leu Ile
2385 2390 2395 2400
Cys Ala Met Gly Leu Phe Val His Glu Phe Phe Tyr Ser Leu Leu Leu
2405 2410 2415
Phe Asp Leu Val Tyr Arg Glu Glu Thr Leu Leu Asn Val Ile Lys Ser
2420 2425 2430
Val Thr Arg Asn Gly Arg Pro Ile Ile Leu Thr Ala Ala Leu Ala Leu
2435 2440 2445
Ile Leu Val Tyr Leu Phe Ser Ile Val Gly Tyr Leu Phe Phe Lys Asp
2450 2455 2460
Asp Phe Ile Leu Glu Val Asp Arg Leu Pro Asn Glu Thr Ala Gly Pro
2465 2470 2475 2480
Glu Thr Gly Glu Ser Leu Ala Asn Asp Phe Leu Tyr Ser Asp Val Cys
2485 2490 2495
Arg Val Glu Thr Gly Glu Asn Cys Thr Ser Pro Ala Pro Lys Glu Glu
2500 2505 2510
Leu Leu Pro Val Glu Glu Thr Glu Gln Asp Lys Glu His Thr Cys Glu
2515 2520 2525
Thr Leu Leu Met Cys Ile Val Thr Val Leu Ser His Gly Leu Arg Ser
2530 2535 2540
Gly Gly Gly Val Gly Asp Val Leu Arg Lys Pro Ser Lys Glu Glu Pro
2545 2550 2555 2560
Leu Phe Ala Ala Arg Val Ile Tyr Asp Leu Leu Phe Phe Phe Met Val
2565 2570 2575
Ile Ile Ile Val Leu Asn Leu Ile Phe Gly Val Ile Ile Asp Thr Phe
2580 2585 2590
Ala Asp Leu Arg Ser Glu Lys Gln Lys Lys Glu Glu Ile Leu Lys Thr
2595 2600 2605
Thr Cys Phe Ile Cys Gly Leu Glu Arg Asp Lys Phe Asp Asn Lys Thr
2610 2615 2620
Val Thr Phe Glu Glu His Ile Lys Glu Glu His Asn Met Trp His Tyr
2625 2630 2635 2640
Leu Cys Phe Ile Val Leu Val Lys Val Lys Asp Ser Thr Glu Tyr Thr
2645 2650 2655

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Gly Pro Glu Ser Tyr Val Ala Glu Met Ile Arg Glu Arg Asn Leu Asp
            2660                2665                2670
Trp Phe Pro Arg Met Arg Ala Met Ser Leu Val Ser Ser Asp Ser Glu
        2675                2680                2685
Gly Glu Gln Asn Glu Leu Arg Asn Leu Gln Glu Lys Leu Glu Ser Thr
    2690                2695                2700
Met Lys Leu Val Thr Asn Leu Ser Gly Gln Leu Ser Glu Leu Lys Asp
2705                2710                2715                2720
Gln Met Thr Glu Gln Arg Lys Gln Lys Gln Arg Ile Gly Leu Leu Gly
                2725                2730                2735
His Pro Pro His Met Asn Val Asn Pro Gln Gln Pro Ala
            2740                2745


<210> 11
<211> 2710
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/note =
      synthetic construct

<400> 11
Met Ser Asp Lys Met Ser Ser Phe Leu His Ile Gly Asp Ile Cys Ser
 1               5                  10                  15
Leu Tyr Ala Glu Gly Ser Thr Asn Gly Phe Ile Ser Thr Leu Gly Leu
            20                  25                  30
Val Asp Asp Arg Cys Val Val Gln Pro Glu Ala Gly Asp Leu Asn Asn
        35                  40                  45
Pro Pro Lys Lys Phe Arg Asp Cys Leu Phe Lys Leu Cys Pro Met Asn
    50                  55                  60
Arg Tyr Ser Ala Gln Lys Gln Phe Trp Lys Ala Ala Lys Pro Gly Ala
65                  70                  75                  80
Asn Ser Thr Thr Asp Ala Val Leu Leu Asn Lys Leu His His Ala Ala
                85                  90                  95
Asp Leu Glu Lys Lys Gln Asn Glu Thr Glu Asn Arg Lys Leu Leu Gly
            100                 105                 110
Thr Val Ile Gln Tyr Gly Asn Val Ile Gln Leu Leu His Leu Lys Ser
        115                 120                 125
Asn Lys Tyr Leu Thr Val Asn Lys Arg Leu Pro Ala Leu Leu Glu Lys
    130                 135                 140
Asn Ala Met Arg Val Thr Leu Asp Glu Ala Gly Asn Glu Gly Ser Trp
145                 150                 155                 160
Phe Tyr Ile Gln Pro Phe Tyr Lys Leu Arg Ser Ile Gly Asp Ser Val
                165                 170                 175
Val Ile Gly Asp Lys Val Val Leu Asn Pro Val Asn Ala Gly Gln Pro
            180                 185                 190
Leu His Ala Ser Ser His Gln Leu Val Asp Asn Pro Gly Cys Asn Glu
        195                 200                 205
Val Asn Ser Val Asn Cys Asn Thr Ser Trp Lys Ile Val Leu Phe Met
    210                 215                 220
Lys Trp Ser Asp Asn Lys Asp Asp Ile Leu Lys Gly Gly Asp Val Val
225                 230                 235                 240
Arg Leu Phe His Ala Glu Gln Glu Lys Phe Leu Thr Cys Asp Glu His
                245                 250                 255
Arg Lys Lys Gln His Val Phe Leu Arg Thr Thr Gly Arg Gln Ser Ala
            260                 265                 270
Thr Ser Ala Thr Ser Ser Lys Ala Leu Trp Glu Val Glu Val Val Gln
        275                 280                 285
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His Asp Pro Cys Arg Gly Gly Ala Gly Tyr Trp Asn Ser Leu Phe Arg
    290                 295                 300
Phe Lys His Leu Ala Thr Gly His Tyr Leu Ala Ala Glu Val Asp Pro
305                 310                 315                 320
Asp Phe Glu Glu Glu Cys Leu Glu Phe Gln Pro Ser Val Asp Pro Asp
                325                 330                 335
Gln Asp Ala Ser Arg Ser Arg Leu Arg Asn Ala Gln Glu Lys Met Val
            340                 345                 350
Tyr Ser Leu Val Ser Val Pro Glu Gly Asn Asp Ile Ser Ser Ile Phe
        355                 360                 365
Glu Leu Asp Pro Thr Thr Leu Arg Gly Gly Asp Ser Leu Val Pro Arg
    370                 375                 380
Asn Ser Tyr Val Arg Leu Arg His Leu Cys Thr Asn Thr Trp Val His
385                 390                 395                 400
Ser Thr Asn Ile Pro Ile Asp Lys Glu Glu Glu Lys Pro Val Met Leu
                405                 410                 415
Lys Ile Gly Thr Ser Pro Leu Lys Glu Asp Lys Glu Ala Phe Ala Ile
            420                 425                 430
Val Pro Val Ser Pro Ala Glu Val Arg Asp Leu Asp Phe Ala Asn Asp
        435                 440                 445
Ala Ser Lys Val Leu Gly Ser Ile Ala Gly Lys Leu Glu Lys Gly Thr
    450                 455                 460
Ile Thr Gln Asn Glu Arg Arg Ser Val Thr Lys Leu Leu Glu Asp Leu
465                 470                 475                 480
Val Tyr Phe Val Thr Gly Gly Thr Asn Ser Gly Gln Asp Val Leu Glu
                485                 490                 495
Val Val Phe Ser Lys Pro Asn Arg Glu Arg Gln Lys Leu Met Arg Glu
            500                 505                 510
Gln Asn Ile Leu Lys Gln Ile Phe Lys Leu Leu Gln Ala Pro Phe Thr
        515                 520                 525
Asp Cys Gly Asp Gly Pro Met Leu Arg Leu Glu Glu Leu Gly Asp Gln
    530                 535                 540
Arg His Ala Pro Phe Arg His Ile Cys Arg Leu Cys Tyr Arg Val Leu
545                 550                 555                 560
Arg His Ser Gln Gln Asp Tyr Arg Lys Asn Gln Glu Tyr Ile Ala Lys
                565                 570                 575
Gln Phe Gly Phe Met Gln Lys Gln Ile Gly Tyr Asp Val Leu Ala Glu
            580                 585                 590
Asp Thr Ile Thr Ala Leu Leu His Asn Asn Arg Lys Leu Leu Glu Lys
        595                 600                 605
His Ile Thr Ala Ala Glu Ile Asp Thr Phe Val Ser Leu Val Arg Lys
    610                 615                 620
Asn Arg Glu Pro Arg Phe Leu Asp Tyr Leu Ser Asp Leu Cys Val Ser
625                 630                 635                 640
Met Asn Lys Ser Ile Pro Val Thr Gln Glu Leu Ile Cys Lys Ala Val
                645                 650                 655
Leu Asn Pro Thr Asn Ala Asp Ile Leu Ile Glu Thr Lys Leu Val Leu
            660                 665                 670
Ser Arg Phe Glu Phe Glu Gly Val Ser Thr Gly Glu Asn Ala Leu Glu
        675                 680                 685
Ala Gly Glu Asp Glu Glu Glu Val Trp Leu Phe Trp Arg Asp Ser Asn
    690                 695                 700
Lys Glu Ile Arg Ser Lys Ser Val Arg Glu Leu Ala Gln Asp Ala Lys
705                 710                 715                 720
Glu Gly Gln Lys Glu Asp Arg Asp Val Leu Ser Tyr Tyr Arg Tyr Gln
                725                 730                 735
Leu Asn Leu Phe Ala Arg Met Cys Leu Asp Arg Gln Tyr Leu Ala Ile
            740                 745                 750
Asn Glu Ile Ser Gly Gln Leu Asp Val Asp Leu Ile Leu Arg Cys Met
        755                 760                 765
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```
Ser Asp Glu Asn Leu Pro Tyr Asp Leu Arg Ala Ser Phe Cys Arg Leu
    770                 775                 780
Met Leu His Met His Val Asp Arg Asp Pro Gln Glu Gln Val Thr Pro
785                 790                 795                 800
Val Lys Tyr Ala Arg Leu Trp Ser Glu Ile Pro Ser Glu Ile Ala Ile
                805                 810                 815
Asp Asp Tyr Asp Ser Ser Gly Ala Ser Lys Asp Glu Ile Lys Glu Arg
            820                 825                 830
Phe Ala Gln Thr Met Glu Phe Val Glu Glu Tyr Leu Arg Asp Val Val
        835                 840                 845
Cys Gln Arg Phe Pro Phe Ser Asp Lys Glu Lys Asn Lys Leu Thr Phe
    850                 855                 860
Glu Val Val Asn Leu Ala Arg Asn Leu Ile Tyr Phe Gly Phe Tyr Asn
865                 870                 875                 880
Phe Ser Asp Leu Leu Arg Leu Thr Lys Ile Leu Leu Ala Ile Leu Asp
                885                 890                 895
Cys Val His Val Thr Thr Ile Phe Pro Ile Ser Lys Met Thr Lys Gly
            900                 905                 910
Glu Glu Asn Lys Gly Ser Asn Val Met Arg Ser Ile His Gly Val Gly
        915                 920                 925
Glu Leu Met Thr Gln Val Val Leu Arg Gly Gly Gly Phe Leu Pro Met
    930                 935                 940
Thr Pro Met Ala Ala Ala Pro Glu Gly Asn Val Lys Gln Ala Glu Pro
945                 950                 955                 960
Glu Lys Glu Asp Ile Met Val Met Asp Thr Lys Leu Lys Ile Ile Glu
                965                 970                 975
Ile Leu Gln Phe Ile Leu Asn Val Arg Leu Asp Tyr Arg Ile Ser Cys
            980                 985                 990
Leu Leu Cys Ile Phe Lys Arg Glu Phe Asp Glu Ser Asn Ser Gln Ser
        995                 1000                1005
Ser Glu Thr Ser Ser Gly Asn Ser Ser Gln Glu Gly Pro Ser Asn Val
    1010                1015                1020
Pro Gly Ala Leu Asp Phe Glu His Ile Glu Glu Gln Ala Glu Gly Ile
1025                1030                1035                1040
Phe Gly Gly Ser Glu Glu Asn Thr Pro Leu Asp Leu Asp Asp His Gly
                1045                1050                1055
Gly Arg Thr Phe Leu Arg Val Leu Leu His Leu Thr Met His Asp Tyr
            1060                1065                1070
Pro Pro Leu Val Ser Gly Ala Leu Gln Leu Leu Phe Arg His Phe Ser
        1075                1080                1085
Gln Arg Gln Glu Val Leu Gln Ala Phe Lys Gln Val Gln Leu Leu Val
    1090                1095                1100
Thr Ser Gln Asp Val Asp Asn Tyr Lys Gln Ile Lys Gln Asp Leu Asp
1105                1110                1115                1120
Gln Leu Arg Ser Ile Val Glu Lys Ser Glu Leu Trp Val Tyr Lys Gly
                1125                1130                1135
Gln Gly Pro Asp Glu Pro Met Asp Gly Ala Ser Gly Glu Asn Glu His
            1140                1145                1150
Lys Lys Thr Glu Glu Gly Thr Ser Lys Pro Leu Lys His Glu Ser Thr
        1155                1160                1165
Ser Ser Tyr Asn Tyr Arg Val Val Lys Glu Ile Leu Ile Arg Leu Ser
    1170                1175                1180
Lys Leu Cys Val Gln Glu Ser Ala Ser Val Arg Lys Ser Arg Lys Gln
1185                1190                1195                1200
Gln Gln Arg Leu Leu Arg Asn Met Gly Ala His Ala Val Val Leu Glu
                1205                1210                1215
Leu Leu Gln Ile Pro Tyr Glu Lys Ala Glu Asp Thr Lys Met Gln Glu
            1220                1225                1230
Ile Met Arg Leu Ala His Glu Phe Leu Gln Asn Phe Cys Ala Gly Asn
        1235                1240                1245
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```
Gln Gln Asn Gln Ala Leu Leu His Lys His Ile Asn Leu Phe Leu Asn
    1250                1255                1260
Pro Gly Ile Leu Glu Ala Val Thr Met Gln His Ile Phe Met Asn Asn
1265                1270                1275                1280
Phe Gln Leu Cys Ser Glu Ile Asn Glu Arg Val Val Gln His Phe Val
                1285                1290                1295
His Cys Ile Glu Thr His Gly Arg Asn Val Gln Tyr Ile Lys Phe Leu
            1300                1305                1310
Gln Thr Ile Val Lys Ala Glu Gly Lys Phe Ile Lys Lys Cys Gln Asp
        1315                1320                1325
Met Val Met Ala Glu Leu Val Asn Ser Gly Glu Asp Val Leu Val Phe
    1330                1335                1340
Tyr Asn Asp Arg Ala Ser Phe Gln Thr Leu Ile Gln Met Met Arg Ser
1345                1350                1355                1360
Glu Arg Asp Arg Met Asp Glu Asn Ser Pro Leu Phe Met Tyr His Ile
                1365                1370                1375
His Leu Val Glu Leu Leu Ala Val Cys Thr Glu Gly Lys Asn Val Tyr
            1380                1385                1390
Thr Glu Ile Lys Cys Asn Ser Leu Leu Pro Leu Asp Asp Ile Val Arg
        1395                1400                1405
Val Val Thr His Glu Asp Cys Ile Pro Glu Val Lys Ile Ala Tyr Ile
    1410                1415                1420
Asn Phe Leu Asn His Cys Tyr Val Asp Thr Glu Val Glu Met Lys Glu
1425                1430                1435                1440
Ile Tyr Thr Ser Asn His Met Trp Lys Leu Phe Glu Asn Phe Leu Val
                1445                1450                1455
Asp Ile Cys Arg Ala Cys Asn Asn Thr Ser Asp Arg Lys His Ala Asp
            1460                1465                1470
Ser Val Leu Glu Lys Tyr Val Thr Glu Ile Val Met Ser Ile Val Thr
        1475                1480                1485
Thr Phe Phe Ser Ser Pro Phe Ser Asp Gln Ser Thr Thr Leu Gln Thr
    1490                1495                1500
Arg Gln Pro Val Phe Val Gln Leu Leu Gln Gly Val Phe Arg Val Tyr
1505                1510                1515                1520
His Cys Asn Trp Leu Met Pro Ser Gln Lys Ala Ser Val Glu Ser Cys
                1525                1530                1535
Ile Arg Val Leu Ser Asp Val Ala Lys Ser Arg Ala Ile Ala Ile Pro
            1540                1545                1550
Val Asp Leu Asp Ser Gln Val Asn Asn Leu Phe Leu Lys Ser His Asn
        1555                1560                1565
Ile Val Gln Lys Thr Ala Met Asn Trp Arg Leu Ser Ala Arg Asn Ala
    1570                1575                1580
Ala Arg Arg Asp Asp Val Leu Ala Ala Ser Arg Asp Tyr Arg Asn Ile
1585                1590                1595                1600
Ile Glu Arg Leu Gln Asp Ile Val Ser Ala Leu Glu Asp Arg Leu Arg
                1605                1610                1615
Pro Leu Val Gln Ala Glu Leu Ser Val Leu Val Asp Val Leu His Arg
            1620                1625                1630
Pro Glu Leu Leu Phe Pro Glu Asn Thr Asp Ala Arg Arg Lys Cys Glu
        1635                1640                1645
Ser Gly Gly Phe Ile Cys Lys Leu Ile Lys His Thr Lys Gln Leu Leu
    1650                1655                1660
Glu Glu Asn Glu Glu Lys Leu Cys Ile Lys Val Leu Gln Thr Leu Arg
1665                1670                1675                1680
Glu Met Met Thr Lys Asp Arg Gly Tyr Gly Glu Lys Gly Glu Ala Leu
                1685                1690                1695
Arg Gln Ile Leu Val Asn Arg Tyr Tyr Gly Asn Ile Arg Pro Ser Gly
            1700                1705                1710
Arg Arg Glu Asp Leu Thr Ser Phe Gly Asn Gly Pro Leu Ser Pro Gly
        1715                1720                1725
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Gly Pro Ser Lys Pro Gly Gly Gly Gly Gly Gly Pro Gly Ser Gly Ser
    1730                1735                1740
Thr Ser Arg Gly Glu Met Ser Leu Ala Glu Val Gln Cys His Leu Asp
1745                1750                1755                1760
Lys Glu Gly Ala Ser Asn Leu Val Ile Asp Leu Ile Met Asn Ala Ser
                1765                1770                1775
Ser Asp Arg Val Phe His Glu Ser Ile Leu Leu Ala Ile Ala Leu Leu
            1780                1785                1790
Glu Gly Gly Asn Thr Thr Ile Gln His Ser Phe Phe Cys Arg Leu Thr
        1795                1800                1805
Glu Asp Lys Lys Ser Glu Lys Phe Phe Lys Val Phe Tyr Asp Arg Met
    1810                1815                1820
Lys Val Ala Gln Gln Glu Ile Lys Ala Thr Val Thr Val Asn Thr Ser
1825                1830                1835                1840
Asp Leu Gly Asn Lys Lys Lys Asp Asp Glu Val Asp Arg Asp Ala Pro
                1845                1850                1855
Ser Arg Lys Lys Ala Lys Glu Pro Thr Thr Gln Ile Thr Glu Glu Val
            1860                1865                1870
Arg Asp Gln Leu Leu Glu Ala Ser Ala Ala Thr Arg Lys Ala Phe Thr
        1875                1880                1885
Thr Phe Arg Arg Glu Ala Asp Pro Asp Asp His Tyr Gln Ser Gly Glu
    1890                1895                1900
Gly Thr Gln Ala Thr Thr Asp Lys Ala Lys Asp Asp Leu Glu Met Ser
1905                1910                1915                1920
Ala Val Ile Thr Ile Met Gln Pro Ile Leu Arg Phe Leu Gln Leu Leu
                1925                1930                1935
Cys Glu Asn His Asn Arg Asp Leu Gln Asn Phe Leu Arg Cys Gln Asn
            1940                1945                1950
Asn Lys Thr Asn Tyr Asn Leu Val Cys Glu Thr Leu Gln Phe Leu Asp
        1955                1960                1965
Cys Ile Cys Gly Ser Thr Thr Gly Gly Leu Gly Leu Leu Gly Leu Tyr
    1970                1975                1980
Ile Asn Glu Lys Asn Val Ala Leu Ile Asn Gln Thr Leu Glu Ser Leu
1985                1990                1995                2000
Thr Glu Tyr Cys Gln Gly Pro Cys His Glu Asn Gln Asn Cys Ile Ala
                2005                2010                2015
Thr His Glu Ser Asn Gly Ile Asp Ile Ile Thr Ala Leu Ile Leu Asn
            2020                2025                2030
Asp Ile Asn Pro Leu Gly Lys Lys Arg Met Asp Leu Val Leu Glu Leu
        2035                2040                2045
Lys Asn Asn Ala Ser Lys Leu Leu Leu Ala Ile Met Glu Ser Arg His
    2050                2055                2060
Asp Ser Glu Asn Ala Glu Arg Ile Leu Tyr Asn Met Arg Pro Lys Glu
2065                2070                2075                2080
Leu Val Glu Val Ile Lys Lys Ala Tyr Met Gln Gly Glu Val Glu Phe
                2085                2090                2095
Glu Asp Gly Glu Asn Gly Glu Asp Gly Ala Ala Ser Pro Arg Asn Val
            2100                2105                2110
Gly His Asn Ile Tyr Ile Leu Ala His Gln Leu Ala Arg His Asn Lys
        2115                2120                2125
Glu Leu Gln Thr Met Leu Lys Pro Gly Gly Gln Val Asp Gly Asp Glu
    2130                2135                2140
Ala Leu Glu Phe Tyr Ala Lys His Thr Ala Gln Ile Glu Ile Val Arg
2145                2150                2155                2160
Leu Asp Arg Thr Met Glu Gln Ile Val Phe Pro Val Pro Ser Ile Cys
                2165                2170                2175
Glu Phe Leu Thr Lys Glu Ser Lys Leu Arg Ile Tyr Tyr Thr Thr Glu
            2180                2185                2190
Arg Asp Glu Gln Gly Ser Lys Ile Asn Asp Phe Phe Leu Arg Ser Glu
        2195                2200                2205
```

```
Asp Leu Phe Asn Glu Met Asn Trp Gln Lys Lys Leu Arg Ala Gln Pro
    2210                2215                2220
Val Leu Tyr Trp Cys Ala Arg Asn Met Ser Phe Trp Ser Ser Ile Ser
2225                2230                2235                2240
Phe Asn Leu Ala Val Leu Met Asn Leu Leu Val Ala Phe Phe Tyr Pro
                2245                2250                2255
Phe Lys Gly Val Arg Gly Gly Thr Leu Glu Pro His Trp Ser Gly Leu
            2260                2265                2270
Leu Trp Thr Ala Met Leu Ile Ser Leu Ala Ile Val Ile Ala Leu Pro
        2275                2280                2285
Lys Pro His Gly Ile Arg Ala Leu Ile Ala Ser Thr Ile Leu Arg Leu
    2290                2295                2300
Ile Phe Ser Val Gly Leu Gln Pro Thr Leu Phe Leu Leu Gly Ala Phe
2305                2310                2315                2320
Asn Val Cys Asn Lys Ile Ile Phe Leu Met Ser Phe Val Gly Asn Cys
                2325                2330                2335
Gly Thr Phe Thr Arg Gly Tyr Arg Ala Met Val Leu Asp Val Glu Phe
            2340                2345                2350
Leu Tyr His Leu Leu Tyr Leu Leu Ile Cys Ala Met Gly Leu Phe Val
        2355                2360                2365
His Glu Phe Phe Tyr Ser Leu Leu Leu Phe Asp Leu Val Tyr Arg Glu
    2370                2375                2380
Glu Thr Leu Leu Asn Val Ile Lys Ser Val Thr Arg Asn Gly Arg Pro
2385                2390                2395                2400
Ile Ile Leu Thr Ala Ala Leu Ala Leu Ile Leu Val Tyr Leu Phe Ser
                2405                2410                2415
Ile Val Gly Tyr Leu Phe Phe Lys Asp Asp Phe Ile Leu Glu Val Asp
            2420                2425                2430
Arg Leu Pro Asn Glu Thr Ala Gly Pro Glu Thr Gly Glu Ser Leu Ala
        2435                2440                2445
Asn Asp Phe Leu Tyr Ser Asp Val Cys Arg Val Glu Thr Gly Glu Asn
    2450                2455                2460
Cys Thr Ser Pro Ala Pro Lys Glu Glu Leu Leu Pro Val Glu Glu Thr
2465                2470                2475                2480
Glu Gln Asp Lys Glu His Thr Cys Glu Thr Leu Leu Met Cys Ile Val
                2485                2490                2495
Thr Val Leu Ser His Gly Leu Arg Ser Gly Gly Gly Val Gly Asp Val
            2500                2505                2510
Leu Arg Lys Pro Ser Lys Glu Glu Pro Leu Phe Ala Ala Arg Val Ile
        2515                2520                2525
Tyr Asp Leu Leu Phe Phe Phe Met Val Ile Ile Ile Val Leu Asn Leu
    2530                2535                2540
Ile Phe Gly Val Ile Ile Asp Thr Phe Ala Asp Leu Arg Ser Glu Lys
2545                2550                2555                2560
Gln Lys Lys Glu Glu Ile Leu Lys Thr Thr Cys Phe Ile Cys Gly Leu
                2565                2570                2575
Glu Arg Asp Lys Phe Asp Asn Lys Thr Val Thr Phe Glu Glu His Ile
            2580                2585                2590
Lys Glu Glu His Asn Met Trp His Tyr Leu Cys Phe Ile Val Leu Val
        2595                2600                2605
Lys Val Lys Asp Ser Thr Glu Tyr Thr Gly Pro Glu Ser Tyr Val Ala
    2610                2615                2620
Glu Met Ile Arg Glu Arg Asn Leu Asp Trp Phe Pro Arg Met Arg Ala
2625                2630                2635                2640
Met Ser Leu Val Ser Ser Asp Ser Glu Gly Glu Gln Asn Glu Leu Arg
                2645                2650                2655
Asn Leu Gln Glu Lys Leu Glu Ser Thr Met Lys Leu Val Thr Asn Leu
            2660                2665                2670
Ser Gly Gln Leu Ser Glu Leu Lys Asp Gln Met Thr Glu Gln Arg Lys
        2675                2680                2685
```

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Gln Lys Gln Arg Ile Gly Leu Leu Gly His Pro Pro His Met Asn Val
    2690                2695                2700
Asn Pro Gln Gln Pro Ala
2705                2710


<210> 12
<211> 2749
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/note =
      synthetic construct

<400> 12
Met Ser Asp Lys Met Ser Ser Phe Leu His Ile Gly Asp Ile Cys Ser
 1               5                  10                  15
Leu Tyr Ala Glu Gly Ser Thr Asn Gly Phe Ile Ser Thr Leu Gly Leu
            20                  25                  30
Val Asp Asp Arg Cys Val Val Gln Pro Glu Ala Gly Asp Leu Asn Asn
        35                  40                  45
Pro Pro Lys Lys Phe Arg Asp Cys Leu Phe Lys Leu Cys Pro Met Asn
    50                  55                  60
Arg Tyr Ser Ala Gln Lys Gln Phe Trp Lys Ala Ala Lys Pro Gly Ala
65                  70                  75                  80
Asn Ser Thr Thr Asp Ala Val Leu Leu Asn Lys Leu His His Ala Ala
                85                  90                  95
Asp Leu Glu Lys Lys Gln Asn Glu Thr Glu Asn Arg Lys Leu Leu Gly
            100                 105                 110
Thr Val Ile Gln Tyr Gly Asn Val Ile Gln Leu Leu His Leu Lys Ser
        115                 120                 125
Asn Lys Tyr Leu Thr Val Asn Lys Arg Leu Pro Ala Leu Leu Glu Lys
    130                 135                 140
Asn Ala Met Arg Val Thr Leu Asp Glu Ala Gly Asn Glu Gly Ser Trp
145                 150                 155                 160
Phe Tyr Ile Gln Pro Phe Tyr Lys Leu Arg Ser Ile Gly Asp Ser Val
                165                 170                 175
Val Ile Gly Asp Lys Val Val Leu Asn Pro Val Asn Ala Gly Gln Pro
            180                 185                 190
Leu His Ala Ser Ser His Gln Leu Val Asp Asn Pro Gly Cys Asn Glu
        195                 200                 205
Val Asn Ser Val Asn Cys Asn Thr Ser Trp Lys Ile Val Leu Phe Met
    210                 215                 220
Lys Trp Ser Asp Asn Lys Asp Asp Ile Leu Lys Gly Gly Asp Val Val
225                 230                 235                 240
Arg Leu Phe His Ala Glu Gln Glu Lys Phe Leu Thr Cys Asp Glu His
                245                 250                 255
Arg Lys Lys Gln His Val Phe Leu Arg Thr Thr Gly Arg Gln Ser Ala
            260                 265                 270
Thr Ser Ala Thr Ser Ser Lys Ala Leu Trp Glu Val Glu Val Val Gln
        275                 280                 285
His Asp Pro Cys Arg Gly Gly Ala Gly Tyr Trp Asn Ser Leu Phe Arg
    290                 295                 300
Phe Lys His Leu Ala Thr Gly His Tyr Leu Ala Ala Glu Val Asp Pro
305                 310                 315                 320
Asp Phe Glu Glu Glu Cys Leu Glu Phe Gln Pro Ser Val Asp Pro Asp
                325                 330                 335
Gln Asp Ala Ser Arg Ser Arg Leu Arg Asn Ala Gln Glu Lys Met Val
            340                 345                 350
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Tyr Ser Leu Val Ser Val Pro Glu Gly Asn Asp Ile Ser Ser Ile Phe
        355                 360                 365
Glu Leu Asp Pro Thr Thr Leu Arg Gly Gly Asp Ser Leu Val Pro Arg
    370                 375                 380
Asn Ser Tyr Val Arg Leu Arg His Leu Cys Thr Asn Thr Trp Val His
385                 390                 395                 400
Ser Thr Asn Ile Pro Ile Asp Lys Glu Glu Glu Lys Pro Val Met Leu
                405                 410                 415
Lys Ile Gly Thr Ser Pro Leu Lys Glu Asp Lys Glu Ala Phe Ala Ile
            420                 425                 430
Val Pro Val Ser Pro Ala Glu Val Arg Asp Leu Asp Phe Ala Asn Asp
        435                 440                 445
Ala Ser Lys Val Leu Gly Ser Ile Ala Gly Lys Leu Glu Lys Gly Thr
    450                 455                 460
Ile Thr Gln Asn Glu Arg Arg Ser Val Thr Lys Leu Leu Glu Asp Leu
465                 470                 475                 480
Val Tyr Phe Val Thr Gly Gly Thr Asn Ser Gly Gln Asp Val Leu Glu
                485                 490                 495
Val Val Phe Ser Lys Pro Asn Arg Glu Arg Gln Lys Leu Met Arg Glu
            500                 505                 510
Gln Asn Ile Leu Lys Gln Ile Phe Lys Leu Leu Gln Ala Pro Phe Thr
        515                 520                 525
Asp Cys Gly Asp Gly Pro Met Leu Arg Leu Glu Glu Leu Gly Asp Gln
    530                 535                 540
Arg His Ala Pro Phe Arg His Ile Cys Arg Leu Cys Tyr Arg Val Leu
545                 550                 555                 560
Arg His Ser Gln Gln Asp Tyr Arg Lys Asn Gln Glu Tyr Ile Ala Lys
                565                 570                 575
Gln Phe Gly Phe Met Gln Lys Gln Ile Gly Tyr Asp Val Leu Ala Glu
            580                 585                 590
Asp Thr Ile Thr Ala Leu Leu His Asn Asn Arg Lys Leu Leu Glu Lys
        595                 600                 605
His Ile Thr Ala Ala Glu Ile Asp Thr Phe Val Ser Leu Val Arg Lys
    610                 615                 620
Asn Arg Glu Pro Arg Phe Leu Asp Tyr Leu Ser Asp Leu Cys Val Ser
625                 630                 635                 640
Met Asn Lys Ser Ile Pro Val Thr Gln Glu Leu Ile Cys Lys Ala Val
                645                 650                 655
Leu Asn Pro Thr Asn Ala Asp Ile Leu Ile Glu Thr Lys Leu Val Leu
            660                 665                 670
Ser Arg Phe Glu Phe Glu Gly Val Ser Thr Gly Glu Asn Ala Leu Glu
        675                 680                 685
Ala Gly Glu Asp Glu Glu Glu Val Trp Leu Phe Trp Arg Asp Ser Asn
    690                 695                 700
Lys Glu Ile Arg Ser Lys Ser Val Arg Glu Leu Ala Gln Asp Ala Lys
705                 710                 715                 720
Glu Gly Gln Lys Glu Asp Arg Asp Val Leu Ser Tyr Tyr Arg Tyr Gln
                725                 730                 735
Leu Asn Leu Phe Ala Arg Met Cys Leu Asp Arg Gln Tyr Leu Ala Ile
            740                 745                 750
Asn Glu Ile Ser Gly Gln Leu Asp Val Asp Leu Ile Leu Arg Cys Met
        755                 760                 765
Ser Asp Glu Asn Leu Pro Tyr Asp Leu Arg Ala Ser Phe Cys Arg Leu
    770                 775                 780
Met Leu His Met His Val Asp Arg Asp Pro Gln Glu Gln Val Thr Pro
785                 790                 795                 800
Val Lys Tyr Ala Arg Leu Trp Ser Glu Ile Pro Ser Glu Ile Ala Ile
                805                 810                 815
Asp Asp Tyr Asp Ser Ser Gly Ala Ser Lys Asp Glu Ile Lys Glu Arg
            820                 825                 830
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Phe Ala Gln Thr Met Glu Phe Val Glu Glu Tyr Leu Arg Asp Val Val
        835                 840                 845
Cys Gln Arg Phe Pro Phe Ser Asp Lys Glu Lys Asn Lys Leu Thr Phe
    850                 855                 860
Glu Val Val Asn Leu Ala Arg Asn Leu Ile Tyr Phe Gly Phe Tyr Asn
865                 870                 875                 880
Phe Ser Asp Leu Leu Arg Leu Thr Lys Ile Leu Leu Ala Ile Leu Asp
                885                 890                 895
Cys Val His Val Thr Thr Ile Phe Pro Ile Ser Lys Met Thr Lys Gly
            900                 905                 910
Glu Glu Asn Lys Gly Ser Asn Val Met Arg Ser Ile His Gly Val Gly
        915                 920                 925
Glu Leu Met Thr Gln Val Val Leu Arg Gly Gly Gly Phe Leu Pro Met
    930                 935                 940
Thr Pro Met Ala Ala Ala Pro Glu Gly Asn Val Lys Gln Ala Glu Pro
945                 950                 955                 960
Glu Lys Glu Asp Ile Met Val Met Asp Thr Lys Leu Lys Ile Ile Glu
                965                 970                 975
Ile Leu Gln Phe Ile Leu Asn Val Arg Leu Asp Tyr Arg Ile Ser Cys
            980                 985                 990
Leu Leu Cys Ile Phe Lys Arg Glu Phe Asp Glu Ser Asn Ser Gln Ser
        995                 1000                1005
Ser Glu Thr Ser Ser Gly Asn Ser Ser Gln Glu Gly Pro Ser Asn Val
    1010                1015                1020
Pro Gly Ala Leu Asp Phe Glu His Ile Glu Glu Gln Ala Glu Gly Ile
1025                1030                1035                1040
Phe Gly Gly Ser Glu Glu Asn Thr Pro Leu Asp Leu Asp Asp His Gly
                1045                1050                1055
Gly Arg Thr Phe Leu Arg Val Leu Leu His Leu Thr Met His Asp Tyr
            1060                1065                1070
Pro Pro Leu Val Ser Gly Ala Leu Gln Leu Leu Phe Arg His Phe Ser
        1075                1080                1085
Gln Arg Gln Glu Val Leu Gln Ala Phe Lys Gln Val Gln Leu Leu Val
    1090                1095                1100
Thr Ser Gln Asp Val Asp Asn Tyr Lys Gln Ile Lys Gln Asp Leu Asp
1105                1110                1115                1120
Gln Leu Arg Ser Ile Val Glu Lys Ser Glu Leu Trp Val Tyr Lys Gly
                1125                1130                1135
Gln Gly Pro Asp Glu Pro Met Asp Gly Ala Ser Gly Glu Asn Glu His
            1140                1145                1150
Lys Lys Thr Glu Glu Gly Thr Ser Lys Pro Leu Lys His Glu Ser Thr
        1155                1160                1165
Ser Ser Tyr Asn Tyr Arg Val Val Lys Glu Ile Leu Ile Arg Leu Ser
    1170                1175                1180
Lys Leu Cys Val Gln Glu Ser Ala Ser Val Arg Lys Ser Arg Lys Gln
1185                1190                1195                1200
Gln Gln Arg Leu Leu Arg Asn Met Gly Ala His Ala Val Val Leu Glu
                1205                1210                1215
Leu Leu Gln Ile Pro Tyr Glu Lys Ala Glu Asp Thr Lys Met Gln Glu
            1220                1225                1230
Ile Met Arg Leu Ala His Glu Phe Leu Gln Asn Phe Cys Ala Gly Asn
        1235                1240                1245
Gln Gln Asn Gln Ala Leu Leu His Lys His Ile Asn Leu Phe Leu Asn
    1250                1255                1260
Pro Gly Ile Leu Glu Ala Val Thr Met Gln His Ile Phe Met Asn Asn
1265                1270                1275                1280
Phe Gln Leu Cys Ser Glu Ile Asn Glu Arg Val Val Gln His Phe Val
                1285                1290                1295
His Cys Ile Glu Thr His Gly Arg Asn Val Gln Tyr Ile Lys Phe Leu
            1300                1305                1310
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Gln Thr Ile Val Lys Ala Glu Gly Lys Phe Ile Lys Lys Cys Gln Asp
        1315                1320                1325
Met Val Met Ala Glu Leu Val Asn Ser Gly Glu Asp Val Leu Val Phe
    1330                1335                1340
Tyr Asn Asp Arg Ala Ser Phe Gln Thr Leu Ile Gln Met Met Arg Ser
1345                1350                1355                1360
Glu Arg Asp Arg Met Asp Glu Asn Ser Pro Leu Phe Met Tyr His Ile
                1365                1370                1375
His Leu Val Glu Leu Leu Ala Val Cys Thr Glu Gly Lys Asn Val Tyr
            1380                1385                1390
Thr Glu Ile Lys Cys Asn Ser Leu Leu Pro Leu Asp Asp Ile Val Arg
        1395                1400                1405
Val Val Thr His Glu Asp Cys Ile Pro Glu Val Lys Ile Ala Tyr Ile
    1410                1415                1420
Asn Phe Leu Asn His Cys Tyr Val Asp Thr Glu Val Glu Met Lys Glu
1425                1430                1435                1440
Ile Tyr Thr Ser Asn His Met Trp Lys Leu Phe Glu Asn Phe Leu Val
                1445                1450                1455
Asp Ile Cys Arg Ala Cys Asn Asn Thr Ser Asp Arg Lys His Ala Asp
            1460                1465                1470
Ser Val Leu Glu Lys Tyr Val Thr Glu Ile Val Met Ser Ile Val Thr
        1475                1480                1485
Thr Phe Phe Ser Ser Pro Phe Ser Asp Gln Ser Thr Thr Leu Gln Thr
    1490                1495                1500
Arg Gln Pro Val Phe Val Gln Leu Leu Gln Gly Val Phe Arg Val Tyr
1505                1510                1515                1520
His Cys Asn Trp Leu Met Pro Ser Gln Lys Ala Ser Val Glu Ser Cys
                1525                1530                1535
Ile Arg Val Leu Ser Asp Val Ala Lys Ser Arg Ala Ile Ala Ile Pro
            1540                1545                1550
Val Asp Leu Asp Ser Gln Val Asn Asn Leu Phe Leu Lys Ser His Asn
        1555                1560                1565
Ile Val Gln Lys Thr Ala Met Asn Trp Arg Leu Ser Ala Arg Asn Ala
    1570                1575                1580
Ala Arg Arg Asp Asp Val Leu Ala Ala Ser Arg Asp Tyr Arg Asn Ile
1585                1590                1595                1600
Ile Glu Arg Leu Gln Asp Ile Val Ser Ala Leu Glu Asp Arg Leu Arg
                1605                1610                1615
Pro Leu Val Gln Ala Glu Leu Ser Val Leu Val Asp Val Leu His Arg
            1620                1625                1630
Pro Glu Leu Leu Phe Pro Glu Asn Thr Asp Ala Arg Arg Lys Cys Glu
        1635                1640                1645
Ser Gly Gly Phe Ile Cys Lys Leu Ile Lys His Thr Lys Gln Leu Leu
    1650                1655                1660
Glu Glu Asn Glu Glu Lys Leu Cys Ile Lys Val Leu Gln Thr Leu Arg
1665                1670                1675                1680
Glu Met Met Thr Lys Asp Arg Gly Tyr Gly Glu Lys Gln Ile Ser Ile
                1685                1690                1695
Asp Glu Leu Glu Asn Ala Glu Leu Pro Gln Pro Pro Glu Ala Glu Asn
            1700                1705                1710
Ser Thr Glu Glu Leu Glu Pro Ser Pro Pro Leu Arg Gln Leu Glu Asp
        1715                1720                1725
His Lys Arg Gly Glu Ala Leu Arg Gln Ile Leu Val Asn Arg Tyr Tyr
    1730                1735                1740
Gly Asn Ile Arg Pro Ser Gly Arg Arg Glu Asp Leu Thr Ser Phe Gly
1745                1750                1755                1760
Asn Gly Pro Leu Ser Pro Gly Gly Pro Ser Lys Pro Gly Gly Gly Gly
                1765                1770                1775
Gly Gly Pro Gly Ser Gly Ser Thr Ser Arg Gly Glu Met Ser Leu Ala
            1780                1785                1790
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Glu Val Gln Cys His Leu Asp Lys Glu Gly Ala Ser Asn Leu Val Ile
        1795                1800                1805
Asp Leu Ile Met Asn Ala Ser Ser Asp Arg Val Phe His Glu Ser Ile
    1810                1815                1820
Leu Leu Ala Ile Ala Leu Leu Glu Gly Gly Asn Thr Thr Ile Gln His
1825                1830                1835                1840
Ser Phe Phe Cys Arg Leu Thr Glu Asp Lys Lys Ser Glu Lys Phe Phe
                1845                1850                1855
Lys Val Phe Tyr Asp Arg Met Lys Val Ala Gln Gln Glu Ile Lys Ala
            1860                1865                1870
Thr Val Thr Val Asn Thr Ser Asp Leu Gly Asn Lys Lys Lys Asp Asp
        1875                1880                1885
Glu Val Asp Arg Asp Ala Pro Ser Arg Lys Lys Ala Lys Glu Pro Thr
    1890                1895                1900
Thr Gln Ile Thr Glu Glu Val Arg Asp Gln Leu Leu Glu Ala Ser Ala
1905                1910                1915                1920
Ala Thr Arg Lys Ala Phe Thr Thr Phe Arg Arg Glu Ala Asp Pro Asp
                1925                1930                1935
Asp His Tyr Gln Ser Gly Glu Gly Thr Gln Ala Thr Thr Asp Lys Ala
            1940                1945                1950
Lys Asp Asp Leu Glu Met Ser Ala Val Ile Thr Ile Met Gln Pro Ile
        1955                1960                1965
Leu Arg Phe Leu Gln Leu Leu Cys Glu Asn His Asn Arg Asp Leu Gln
    1970                1975                1980
Asn Phe Leu Arg Cys Gln Asn Asn Lys Thr Asn Tyr Asn Leu Val Cys
1985                1990                1995                2000
Glu Thr Leu Gln Phe Leu Asp Cys Ile Cys Gly Ser Thr Thr Gly Gly
                2005                2010                2015
Leu Gly Leu Leu Gly Leu Tyr Ile Asn Glu Lys Asn Val Ala Leu Ile
            2020                2025                2030
Asn Gln Thr Leu Glu Ser Leu Thr Glu Tyr Cys Gln Gly Pro Cys His
        2035                2040                2045
Glu Asn Gln Asn Cys Ile Ala Thr His Glu Ser Asn Gly Ile Asp Ile
    2050                2055                2060
Ile Thr Ala Leu Ile Leu Asn Asp Ile Asn Pro Leu Gly Lys Lys Arg
2065                2070                2075                2080
Met Asp Leu Val Leu Glu Leu Lys Asn Asn Ala Ser Lys Leu Leu Leu
                2085                2090                2095
Ala Ile Met Glu Ser Arg His Asp Ser Glu Asn Ala Glu Arg Ile Leu
            2100                2105                2110
Tyr Asn Met Arg Pro Lys Glu Leu Val Glu Val Ile Lys Lys Ala Tyr
        2115                2120                2125
Met Gln Gly Glu Val Glu Phe Glu Asp Gly Glu Asn Gly Glu Asp Gly
    2130                2135                2140
Ala Ala Ser Pro Arg Asn Val Gly His Asn Ile Tyr Ile Leu Ala His
2145                2150                2155                2160
Gln Leu Ala Arg His Asn Lys Glu Leu Gln Thr Met Leu Lys Pro Gly
                2165                2170                2175
Gly Gln Val Asp Gly Asp Glu Ala Leu Glu Phe Tyr Ala Lys His Thr
            2180                2185                2190
Ala Gln Ile Glu Ile Val Arg Leu Asp Arg Thr Met Glu Gln Ile Val
        2195                2200                2205
Phe Pro Val Pro Ser Ile Cys Glu Phe Leu Thr Lys Glu Ser Lys Leu
    2210                2215                2220
Arg Ile Tyr Tyr Thr Thr Glu Arg Asp Glu Gln Gly Ser Lys Ile Asn
2225                2230                2235                2240
Asp Phe Phe Leu Arg Ser Glu Asp Leu Phe Asn Glu Met Asn Trp Gln
                2245                2250                2255
Lys Lys Leu Arg Ala Gln Pro Val Leu Tyr Trp Cys Ala Arg Asn Met
            2260                2265                2270
```

```
Ser Phe Trp Ser Ser Ile Ser Phe Asn Leu Ala Val Leu Met Asn Leu
        2275                2280                2285
Leu Val Ala Phe Phe Tyr Pro Phe Lys Gly Val Arg Gly Gly Thr Leu
    2290                2295                2300
Glu Pro His Trp Ser Gly Leu Leu Trp Thr Ala Met Leu Ile Ser Leu
2305                2310                2315                2320
Ala Ile Val Ile Ala Leu Pro Lys Pro His Gly Ile Arg Ala Leu Ile
                2325                2330                2335
Ala Ser Thr Ile Leu Arg Leu Ile Phe Ser Val Gly Leu Gln Pro Thr
            2340                2345                2350
Leu Phe Leu Leu Gly Ala Phe Asn Val Cys Asn Lys Ile Ile Phe Leu
        2355                2360                2365
Met Ser Phe Val Gly Asn Cys Gly Thr Phe Thr Arg Gly Tyr Arg Ala
    2370                2375                2380
Met Val Leu Asp Val Glu Phe Leu Tyr His Leu Leu Tyr Leu Leu Ile
2385                2390                2395                2400
Cys Ala Met Gly Leu Phe Val His Glu Phe Phe Tyr Ser Leu Leu Leu
                2405                2410                2415
Phe Asp Leu Val Tyr Arg Glu Glu Thr Leu Leu Asn Val Ile Lys Ser
            2420                2425                2430
Val Thr Arg Asn Gly Arg Pro Ile Ile Leu Thr Ala Ala Leu Ala Leu
        2435                2440                2445
Ile Leu Val Tyr Leu Phe Ser Ile Val Gly Tyr Leu Phe Phe Lys Asp
    2450                2455                2460
Asp Phe Ile Leu Glu Val Asp Arg Leu Pro Asn Glu Thr Ala Gly Pro
2465                2470                2475                2480
Glu Thr Gly Glu Ser Leu Ala Asn Asp Phe Leu Tyr Ser Asp Val Cys
                2485                2490                2495
Arg Val Glu Thr Gly Glu Asn Cys Thr Ser Pro Ala Pro Lys Glu Glu
            2500                2505                2510
Leu Leu Pro Val Glu Glu Thr Glu Gln Asp Lys Glu His Thr Cys Glu
        2515                2520                2525
Thr Leu Leu Met Cys Ile Val Thr Val Leu Ser His Gly Leu Arg Ser
    2530                2535                2540
Gly Gly Gly Val Gly Asp Val Leu Arg Lys Pro Ser Lys Glu Glu Pro
2545                2550                2555                2560
Leu Phe Ala Ala Arg Val Ile Tyr Asp Leu Leu Phe Phe Phe Met Val
                2565                2570                2575
Ile Ile Ile Val Leu Asn Leu Ile Phe Gly Val Ile Ile Asp Thr Phe
            2580                2585                2590
Ala Asp Leu Arg Ser Glu Lys Gln Lys Lys Glu Glu Ile Leu Lys Thr
        2595                2600                2605
Thr Cys Phe Ile Cys Gly Leu Glu Arg Asp Lys Phe Asp Asn Lys Thr
    2610                2615                2620
Val Thr Phe Glu Glu His Ile Lys Glu Glu His Asn Met Trp His Tyr
2625                2630                2635                2640
Leu Cys Phe Ile Val Leu Val Lys Val Lys Asp Ser Thr Glu Tyr Thr
                2645                2650                2655
Gly Pro Glu Ser Tyr Val Ala Glu Met Ile Arg Glu Arg Asn Leu Asp
            2660                2665                2670
Trp Phe Pro Arg Met Arg Ala Met Ser Leu Val Ser Ser Asp Ser Glu
        2675                2680                2685
Gly Glu Gln Asn Glu Leu Arg Asn Leu Gln Glu Lys Leu Glu Ser Thr
    2690                2695                2700
Met Lys Leu Val Thr Asn Leu Ser Gly Gln Leu Ser Glu Leu Lys Asp
2705                2710                2715                2720
Gln Met Thr Glu Gln Arg Lys Gln Lys Gln Arg Ile Gly Leu Leu Gly
                2725                2730                2735
His Pro Pro His Met Asn Val Asn Pro Gln Gln Pro Ala
            2740                2745
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<210> 13
<211> 2710
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/note =
synthetic construct

<400> 13

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Met Ser Asp Lys Met Ser Ser Phe Leu His Ile Gly Asp Ile Cys Ser
 1               5                  10                  15
Leu Tyr Ala Glu Gly Ser Thr Asn Gly Phe Ile Ser Thr Leu Gly Leu
            20                  25                  30
Val Asp Asp Arg Cys Val Val Gln Pro Glu Ala Gly Asp Leu Asn Asn
        35                  40                  45
Pro Pro Lys Lys Phe Arg Asp Cys Leu Phe Lys Leu Cys Pro Met Asn
    50                  55                  60
Arg Tyr Ser Ala Gln Lys Gln Phe Trp Lys Ala Ala Lys Pro Gly Ala
65                  70                  75                  80
Asn Ser Thr Thr Asp Ala Val Leu Leu Asn Lys Leu His His Ala Ala
                85                  90                  95
Asp Leu Glu Lys Lys Gln Asn Glu Thr Glu Asn Arg Lys Leu Leu Gly
            100                 105                 110
Thr Val Ile Gln Tyr Gly Asn Val Ile Gln Leu Leu His Leu Lys Ser
        115                 120                 125
Asn Lys Tyr Leu Thr Val Asn Lys Arg Leu Pro Ala Leu Leu Glu Lys
    130                 135                 140
Asn Ala Met Arg Val Thr Leu Asp Glu Ala Gly Asn Glu Gly Ser Trp
145                 150                 155                 160
Phe Tyr Ile Gln Pro Phe Tyr Lys Leu Arg Ser Ile Gly Asp Ser Val
                165                 170                 175
Val Ile Gly Asp Lys Val Val Leu Asn Pro Val Asn Ala Gly Gln Pro
            180                 185                 190
Leu His Ala Ser Ser His Gln Leu Val Asp Asn Pro Gly Cys Asn Glu
        195                 200                 205
Val Asn Ser Val Asn Cys Asn Thr Ser Trp Lys Ile Val Leu Phe Met
    210                 215                 220
Lys Trp Ser Asp Asn Lys Asp Asp Ile Leu Lys Gly Gly Asp Val Val
225                 230                 235                 240
Arg Leu Phe His Ala Glu Gln Glu Lys Phe Leu Thr Cys Asp Glu His
                245                 250                 255
Arg Lys Lys Gln His Val Phe Leu Arg Thr Thr Gly Arg Gln Ser Ala
            260                 265                 270
Thr Ser Ala Thr Ser Ser Lys Ala Leu Trp Glu Val Glu Val Val Gln
        275                 280                 285
His Asp Pro Cys Arg Gly Gly Ala Gly Tyr Trp Asn Ser Leu Phe Arg
    290                 295                 300
Phe Lys His Leu Ala Thr Gly His Tyr Leu Ala Ala Glu Val Asp Pro
305                 310                 315                 320
Asp Phe Glu Glu Glu Cys Leu Glu Phe Gln Pro Ser Val Asp Pro Asp
                325                 330                 335
Gln Asp Ala Ser Arg Ser Arg Leu Arg Asn Ala Gln Glu Lys Met Val
            340                 345                 350
Tyr Ser Leu Val Ser Val Pro Glu Gly Asn Asp Ile Ser Ser Ile Phe
        355                 360                 365
Glu Leu Asp Pro Thr Thr Leu Arg Gly Gly Asp Ser Leu Val Pro Arg
    370                 375                 380
Asn Ser Tyr Val Arg Leu Arg His Leu Cys Thr Asn Thr Trp Val His
385                 390                 395                 400
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Ser Thr Asn Ile Pro Ile Asp Lys Glu Glu Glu Lys Pro Val Met Leu
                405                 410                 415
Lys Ile Gly Thr Ser Pro Leu Lys Glu Asp Lys Glu Ala Phe Ala Ile
            420                 425                 430
Val Pro Val Ser Pro Ala Glu Val Arg Asp Leu Asp Phe Ala Asn Asp
        435                 440                 445
Ala Ser Lys Val Leu Gly Ser Ile Ala Gly Lys Leu Glu Lys Gly Thr
    450                 455                 460
Ile Thr Gln Asn Glu Arg Arg Ser Val Thr Lys Leu Leu Glu Asp Leu
465                 470                 475                 480
Val Tyr Phe Val Thr Gly Gly Thr Asn Ser Gly Gln Asp Val Leu Glu
                485                 490                 495
Val Val Phe Ser Lys Pro Asn Arg Glu Arg Gln Lys Leu Met Arg Glu
            500                 505                 510
Gln Asn Ile Leu Lys Gln Ile Phe Lys Leu Leu Gln Ala Pro Phe Thr
        515                 520                 525
Asp Cys Gly Asp Gly Pro Met Leu Arg Leu Glu Glu Leu Gly Asp Gln
    530                 535                 540
Arg His Ala Pro Phe Arg His Ile Cys Arg Leu Cys Tyr Arg Val Leu
545                 550                 555                 560
Arg His Ser Gln Gln Asp Tyr Arg Lys Asn Gln Glu Tyr Ile Ala Lys
                565                 570                 575
Gln Phe Gly Phe Met Gln Lys Gln Ile Gly Tyr Asp Val Leu Ala Glu
            580                 585                 590
Asp Thr Ile Thr Ala Leu Leu His Asn Asn Arg Lys Leu Leu Glu Lys
        595                 600                 605
His Ile Thr Ala Ala Glu Ile Asp Thr Phe Val Ser Leu Val Arg Lys
    610                 615                 620
Asn Arg Glu Pro Arg Phe Leu Asp Tyr Leu Ser Asp Leu Cys Val Ser
625                 630                 635                 640
Met Asn Lys Ser Ile Pro Val Thr Gln Glu Leu Ile Cys Lys Ala Val
                645                 650                 655
Leu Asn Pro Thr Asn Ala Asp Ile Leu Ile Glu Thr Lys Leu Val Leu
            660                 665                 670
Ser Arg Phe Glu Phe Glu Gly Val Ser Thr Gly Glu Asn Ala Leu Glu
        675                 680                 685
Ala Gly Glu Asp Glu Glu Glu Val Trp Leu Phe Trp Arg Asp Ser Asn
    690                 695                 700
Lys Glu Ile Arg Ser Lys Ser Val Arg Glu Leu Ala Gln Asp Ala Lys
705                 710                 715                 720
Glu Gly Gln Lys Glu Asp Arg Asp Val Leu Ser Tyr Tyr Arg Tyr Gln
                725                 730                 735
Leu Asn Leu Phe Ala Arg Met Cys Leu Asp Arg Gln Tyr Leu Ala Ile
            740                 745                 750
Asn Glu Ile Ser Gly Gln Leu Asp Val Asp Leu Ile Leu Arg Cys Met
        755                 760                 765
Ser Asp Glu Asn Leu Pro Tyr Asp Leu Arg Ala Ser Phe Cys Arg Leu
    770                 775                 780
Met Leu His Met His Val Asp Arg Asp Pro Gln Glu Gln Val Thr Pro
785                 790                 795                 800
Val Lys Tyr Ala Arg Leu Trp Ser Glu Ile Pro Ser Glu Ile Ala Ile
                805                 810                 815
Asp Asp Tyr Asp Ser Ser Gly Ala Ser Lys Asp Glu Ile Lys Glu Arg
            820                 825                 830
Phe Ala Gln Thr Met Glu Phe Val Glu Glu Tyr Leu Arg Asp Val Val
        835                 840                 845
Cys Gln Arg Phe Pro Phe Ser Asp Lys Glu Lys Asn Lys Leu Thr Phe
    850                 855                 860
Glu Val Val Asn Leu Ala Arg Asn Leu Ile Tyr Phe Gly Phe Tyr Asn
865                 870                 875                 880
```

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Phe Ser Asp Leu Leu Arg Leu Thr Lys Ile Leu Leu Ala Ile Leu Asp
                885                 890                 895
Cys Val His Val Thr Thr Ile Phe Pro Ile Ser Lys Met Thr Lys Gly
            900                 905                 910
Glu Glu Asn Lys Gly Ser Asn Val Met Arg Ser Ile His Gly Val Gly
        915                 920                 925
Glu Leu Met Thr Gln Val Val Leu Arg Gly Gly Gly Phe Leu Pro Met
    930                 935                 940
Thr Pro Met Ala Ala Ala Pro Glu Gly Asn Val Lys Gln Ala Glu Pro
945                 950                 955                 960
Glu Lys Glu Asp Ile Met Val Met Asp Thr Lys Leu Lys Ile Ile Glu
                965                 970                 975
Ile Leu Gln Phe Ile Leu Asn Val Arg Leu Asp Tyr Arg Ile Ser Cys
            980                 985                 990
Leu Leu Cys Ile Phe Lys Arg Glu Phe Asp Glu Ser Asn Ser Gln Ser
        995                 1000                1005
Ser Glu Thr Ser Ser Gly Asn Ser Ser Gln Glu Gly Pro Ser Asn Val
    1010                1015                1020
Pro Gly Ala Leu Asp Phe Glu His Ile Glu Glu Gln Ala Glu Gly Ile
1025                1030                1035                1040
Phe Gly Gly Ser Glu Glu Asn Thr Pro Leu Asp Leu Asp Asp His Gly
                1045                1050                1055
Gly Arg Thr Phe Leu Arg Val Leu Leu His Leu Thr Met His Asp Tyr
            1060                1065                1070
Pro Pro Leu Val Ser Gly Ala Leu Gln Leu Leu Phe Arg His Phe Ser
        1075                1080                1085
Gln Arg Gln Glu Val Leu Gln Ala Phe Lys Gln Val Gln Leu Leu Val
    1090                1095                1100
Thr Ser Gln Asp Val Asp Asn Tyr Lys Gln Ile Lys Gln Asp Leu Asp
1105                1110                1115                1120
Gln Leu Arg Ser Ile Val Glu Lys Ser Glu Leu Trp Val Tyr Lys Gly
                1125                1130                1135
Gln Gly Pro Asp Glu Pro Met Asp Gly Ala Ser Gly Glu Asn Glu His
            1140                1145                1150
Lys Lys Thr Glu Glu Gly Thr Ser Lys Pro Leu Lys His Glu Ser Thr
        1155                1160                1165
Ser Ser Tyr Asn Tyr Arg Val Val Lys Glu Ile Leu Ile Arg Leu Ser
    1170                1175                1180
Lys Leu Cys Val Gln Glu Ser Ala Ser Val Arg Lys Ser Arg Lys Gln
1185                1190                1195                1200
Gln Gln Arg Leu Leu Arg Asn Met Gly Ala His Ala Val Val Leu Glu
                1205                1210                1215
Leu Leu Gln Ile Pro Tyr Glu Lys Ala Glu Asp Thr Lys Met Gln Glu
            1220                1225                1230
Ile Met Arg Leu Ala His Glu Phe Leu Gln Asn Phe Cys Ala Gly Asn
        1235                1240                1245
Gln Gln Asn Gln Ala Leu Leu His Lys His Ile Asn Leu Phe Leu Asn
    1250                1255                1260
Pro Gly Ile Leu Glu Ala Val Thr Met Gln His Ile Phe Met Asn Asn
1265                1270                1275                1280
Phe Gln Leu Cys Ser Glu Ile Asn Glu Arg Val Val Gln His Phe Val
                1285                1290                1295
His Cys Ile Glu Thr His Gly Arg Asn Val Gln Tyr Ile Lys Phe Leu
            1300                1305                1310
Gln Thr Ile Val Lys Ala Glu Gly Lys Phe Ile Lys Lys Cys Gln Asp
        1315                1320                1325
Met Val Met Ala Glu Leu Val Asn Ser Gly Glu Asp Val Leu Val Phe
    1330                1335                1340
Tyr Asn Asp Arg Ala Ser Phe Gln Thr Leu Ile Gln Met Met Arg Ser
1345                1350                1355                1360
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Glu Arg Asp Arg Met Asp Glu Asn Ser Pro Leu Phe Met Tyr His Ile
                1365                1370                1375
His Leu Val Glu Leu Leu Ala Val Cys Thr Glu Gly Lys Asn Val Tyr
            1380                1385                1390
Thr Glu Ile Lys Cys Asn Ser Leu Leu Pro Leu Asp Asp Ile Val Arg
        1395                1400                1405
Val Val Thr His Glu Asp Cys Ile Pro Glu Val Lys Ile Ala Tyr Ile
    1410                1415                1420
Asn Phe Leu Asn His Cys Tyr Val Asp Thr Glu Val Glu Met Lys Glu
1425                1430                1435                1440
Ile Tyr Thr Ser Asn His Met Trp Lys Leu Phe Glu Asn Phe Leu Val
                1445                1450                1455
Asp Ile Cys Arg Ala Cys Asn Asn Thr Ser Asp Arg Lys His Ala Asp
            1460                1465                1470
Ser Val Leu Glu Lys Tyr Val Thr Glu Ile Val Met Ser Ile Val Thr
        1475                1480                1485
Thr Phe Phe Ser Ser Pro Phe Ser Asp Gln Ser Thr Thr Leu Gln Thr
    1490                1495                1500
Arg Gln Pro Val Phe Val Gln Leu Leu Gln Gly Val Phe Arg Val Tyr
1505                1510                1515                1520
His Cys Asn Trp Leu Met Pro Ser Gln Lys Ala Ser Val Glu Ser Cys
                1525                1530                1535
Ile Arg Val Leu Ser Asp Val Ala Lys Ser Arg Ala Ile Ala Ile Pro
            1540                1545                1550
Val Asp Leu Asp Ser Gln Val Asn Asn Leu Phe Leu Lys Ser His Asn
        1555                1560                1565
Ile Val Gln Lys Thr Ala Met Asn Trp Arg Leu Ser Ala Arg Asn Ala
    1570                1575                1580
Ala Arg Arg Asp Asp Val Leu Ala Ala Ser Arg Asp Tyr Arg Asn Ile
1585                1590                1595                1600
Ile Glu Arg Leu Gln Asp Ile Val Ser Ala Leu Glu Asp Arg Leu Arg
                1605                1610                1615
Pro Leu Val Gln Ala Glu Leu Ser Val Leu Val Asp Val Leu His Arg
            1620                1625                1630
Pro Glu Leu Leu Phe Pro Glu Asn Thr Asp Ala Arg Arg Lys Cys Glu
        1635                1640                1645
Ser Gly Gly Phe Ile Cys Lys Leu Ile Lys His Thr Lys Gln Leu Leu
    1650                1655                1660
Glu Glu Asn Glu Glu Lys Leu Cys Ile Lys Val Leu Gln Thr Leu Arg
1665                1670                1675                1680
Glu Met Met Thr Lys Asp Arg Gly Tyr Gly Glu Lys Gly Glu Ala Leu
                1685                1690                1695
Arg Gln Ile Leu Val Asn Arg Tyr Tyr Gly Asn Ile Arg Pro Ser Gly
            1700                1705                1710
Arg Arg Glu Glu Leu Thr Ser Phe Gly Asn Gly Pro Leu Ser Pro Gly
        1715                1720                1725
Gly Pro Ser Lys Pro Gly Gly Gly Gly Gly Gly Pro Gly Ser Gly Ser
    1730                1735                1740
Thr Ser Arg Gly Glu Met Ser Leu Ala Glu Val Gln Cys His Leu Asp
1745                1750                1755                1760
Lys Glu Gly Ala Ser Asn Leu Val Ile Asp Leu Ile Met Asn Ala Ser
                1765                1770                1775
Ser Asp Arg Val Phe His Glu Ser Ile Leu Leu Ala Ile Ala Leu Leu
            1780                1785                1790
Glu Gly Gly Asn Thr Thr Ile Gln His Ser Phe Phe Cys Arg Leu Thr
        1795                1800                1805
Glu Asp Lys Lys Ser Glu Lys Phe Phe Lys Val Phe Tyr Asp Arg Met
    1810                1815                1820
Lys Val Ala Gln Gln Glu Ile Lys Ala Thr Val Thr Val Asn Thr Ser
1825                1830                1835                1840
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Asp Leu Gly Asn Lys Lys Lys Asp Asp Glu Val Asp Arg Asp Ala Pro
                1845                1850                1855
Ser Arg Lys Lys Ala Lys Glu Pro Thr Thr Gln Ile Thr Glu Glu Val
            1860                1865                1870
Arg Asp Gln Leu Leu Glu Ala Ser Ala Ala Thr Arg Lys Ala Phe Thr
        1875                1880                1885
Thr Phe Arg Arg Glu Ala Asp Pro Asp Asp His Tyr Gln Ser Gly Glu
    1890                1895                1900
Gly Thr Gln Ala Thr Thr Asp Lys Ala Lys Asp Asp Leu Glu Met Ser
1905                1910                1915                1920
Ala Val Ile Thr Ile Met Gln Pro Ile Leu Arg Phe Leu Gln Leu Leu
                1925                1930                1935
Cys Glu Asn His Asn Arg Asp Leu Gln Asn Phe Leu Arg Cys Gln Asn
            1940                1945                1950
Asn Lys Thr Asn Tyr Asn Leu Val Cys Glu Thr Leu Gln Phe Leu Asp
        1955                1960                1965
Cys Ile Cys Gly Ser Thr Thr Gly Gly Leu Gly Leu Leu Gly Leu Tyr
    1970                1975                1980
Ile Asn Glu Lys Asn Val Ala Leu Ile Asn Gln Thr Leu Glu Ser Leu
1985                1990                1995                2000
Thr Glu Tyr Cys Gln Gly Pro Cys His Glu Asn Gln Asn Cys Ile Ala
                2005                2010                2015
Thr His Glu Ser Asn Gly Ile Asp Ile Ile Thr Ala Leu Ile Leu Asn
            2020                2025                2030
Asp Ile Asn Pro Leu Gly Lys Lys Arg Met Asp Leu Val Leu Glu Leu
        2035                2040                2045
Lys Asn Asn Ala Ser Lys Leu Leu Leu Ala Ile Met Glu Ser Arg His
    2050                2055                2060
Asp Ser Glu Asn Ala Glu Arg Ile Leu Tyr Asn Met Arg Pro Lys Glu
2065                2070                2075                2080
Leu Val Glu Val Ile Lys Lys Ala Tyr Met Gln Gly Glu Val Glu Phe
                2085                2090                2095
Glu Asp Gly Glu Asn Gly Glu Asp Gly Ala Ala Ser Pro Arg Asn Val
            2100                2105                2110
Gly His Asn Ile Tyr Ile Leu Ala His Gln Leu Ala Arg His Asn Lys
        2115                2120                2125
Glu Leu Gln Thr Met Leu Lys Pro Gly Gly Gln Val Asp Gly Asp Glu
    2130                2135                2140
Ala Leu Glu Phe Tyr Ala Lys His Thr Ala Gln Ile Glu Ile Val Arg
2145                2150                2155                2160
Leu Asp Arg Thr Met Glu Gln Ile Val Phe Pro Val Pro Ser Ile Cys
                2165                2170                2175
Glu Phe Leu Thr Lys Glu Ser Lys Leu Arg Ile Tyr Tyr Thr Thr Glu
            2180                2185                2190
Arg Asp Glu Gln Gly Ser Lys Ile Asn Asp Phe Phe Leu Arg Ser Glu
        2195                2200                2205
Asp Leu Phe Asn Glu Met Asn Trp Gln Lys Lys Leu Arg Ala Gln Pro
    2210                2215                2220
Val Leu Tyr Trp Cys Ala Arg Asn Met Ser Phe Trp Ser Ser Ile Ser
2225                2230                2235                2240
Phe Asn Leu Ala Val Leu Met Asn Leu Leu Val Ala Phe Phe Tyr Pro
                2245                2250                2255
Phe Lys Gly Val Arg Gly Gly Thr Leu Glu Pro His Trp Ser Gly Leu
            2260                2265                2270
Leu Trp Thr Ala Met Leu Ile Ser Leu Ala Ile Val Ile Ala Leu Pro
        2275                2280                2285
Lys Pro His Gly Ile Arg Ala Leu Ile Ala Ser Thr Ile Leu Arg Leu
    2290                2295                2300
Ile Phe Ser Val Gly Leu Gln Pro Thr Leu Phe Leu Leu Gly Ala Phe
2305                2310                2315                2320
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Asn Val Cys Asn Lys Ile Ile Phe Leu Met Ser Phe Val Gly Asn Cys
                2325                2330                2335
Gly Thr Phe Thr Arg Gly Tyr Arg Ala Met Val Leu Asp Val Glu Phe
            2340                2345                2350
Leu Tyr His Leu Leu Tyr Leu Leu Ile Cys Ala Met Gly Leu Phe Val
        2355                2360                2365
His Glu Phe Phe Tyr Ser Leu Leu Leu Phe Asp Leu Val Tyr Arg Glu
    2370                2375                2380
Glu Thr Leu Leu Asn Val Ile Lys Ser Val Thr Arg Asn Gly Arg Pro
2385                2390                2395                2400
Ile Ile Leu Thr Ala Ala Leu Ala Leu Ile Leu Val Tyr Leu Phe Ser
                2405                2410                2415
Ile Val Gly Tyr Leu Phe Phe Lys Asp Asp Phe Ile Leu Glu Val Asp
            2420                2425                2430
Arg Leu Pro Asn Glu Thr Ala Gly Pro Glu Thr Gly Glu Ser Leu Ala
        2435                2440                2445
Asn Asp Phe Leu Tyr Ser Asp Val Cys Arg Val Glu Thr Gly Glu Asn
    2450                2455                2460
Cys Thr Ser Pro Ala Pro Lys Glu Glu Leu Leu Pro Val Glu Glu Thr
2465                2470                2475                2480
Glu Gln Asp Lys Glu His Thr Cys Glu Thr Leu Leu Met Cys Ile Val
                2485                2490                2495
Thr Val Leu Ser His Gly Leu Arg Ser Gly Gly Gly Val Gly Asp Val
            2500                2505                2510
Leu Arg Lys Pro Ser Lys Glu Glu Pro Leu Phe Ala Ala Arg Val Ile
        2515                2520                2525
Tyr Asp Leu Leu Phe Phe Phe Met Val Ile Ile Ile Val Leu Asn Leu
    2530                2535                2540
Ile Phe Gly Val Ile Ile Asp Thr Phe Ala Asp Leu Arg Ser Glu Lys
2545                2550                2555                2560
Gln Lys Lys Glu Glu Ile Leu Lys Thr Thr Cys Phe Ile Cys Gly Leu
                2565                2570                2575
Glu Arg Asp Lys Phe Asp Asn Lys Thr Val Thr Phe Glu Glu His Ile
            2580                2585                2590
Lys Glu Glu His Asn Met Trp His Tyr Leu Cys Phe Ile Val Leu Val
        2595                2600                2605
Lys Val Lys Asp Ser Thr Glu Tyr Thr Gly Pro Glu Ser Tyr Val Ala
    2610                2615                2620
Glu Met Ile Arg Glu Arg Asn Leu Asp Trp Phe Pro Arg Met Arg Ala
2625                2630                2635                2640
Met Ser Leu Val Ser Ser Asp Ser Glu Gly Glu Gln Asn Glu Leu Arg
                2645                2650                2655
Asn Leu Gln Glu Lys Leu Glu Ser Thr Met Lys Leu Val Thr Asn Leu
            2660                2665                2670
Ser Gly Gln Leu Ser Glu Leu Lys Asp Gln Met Thr Glu Gln Arg Lys
        2675                2680                2685
Gln Lys Gln Arg Ile Gly Leu Leu Gly His Pro Pro His Met Asn Val
    2690                2695                2700
Asn Pro Gln Gln Pro Ala
2705                2710
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<210> 14
<211> 2749
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/note =
synthetic construct

<400> 14

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Met Ser Asp Lys Met Ser Ser Phe Leu His Ile Gly Asp Ile Cys Ser
 1               5                  10                  15
Leu Tyr Ala Glu Gly Ser Thr Asn Gly Phe Ile Ser Thr Leu Gly Leu
            20                  25                  30
Val Asp Asp Arg Cys Val Val Gln Pro Glu Ala Gly Asp Leu Asn Asn
        35                  40                  45
Pro Pro Lys Lys Phe Arg Asp Cys Leu Phe Lys Leu Cys Pro Met Asn
    50                  55                  60
Arg Tyr Ser Ala Gln Lys Gln Phe Trp Lys Ala Ala Lys Pro Gly Ala
65                  70                  75                  80
Asn Ser Thr Thr Asp Ala Val Leu Leu Asn Lys Leu His His Ala Ala
                85                  90                  95
Asp Leu Glu Lys Lys Gln Asn Glu Thr Glu Asn Arg Lys Leu Leu Gly
            100                 105                 110
Thr Val Ile Gln Tyr Gly Asn Val Ile Gln Leu Leu His Leu Lys Ser
        115                 120                 125
Asn Lys Tyr Leu Thr Val Asn Lys Arg Leu Pro Ala Leu Leu Glu Lys
    130                 135                 140
Asn Ala Met Arg Val Thr Leu Asp Glu Ala Gly Asn Glu Gly Ser Trp
145                 150                 155                 160
Phe Tyr Ile Gln Pro Phe Tyr Lys Leu Arg Ser Ile Gly Asp Ser Val
                165                 170                 175
Val Ile Gly Asp Lys Val Val Leu Asn Pro Val Asn Ala Gly Gln Pro
            180                 185                 190
Leu His Ala Ser Ser His Gln Leu Val Asp Asn Pro Gly Cys Asn Glu
        195                 200                 205
Val Asn Ser Val Asn Cys Asn Thr Ser Trp Lys Ile Val Leu Phe Met
    210                 215                 220
Lys Trp Ser Asp Asn Lys Asp Asp Ile Leu Lys Gly Gly Asp Val Val
225                 230                 235                 240
Arg Leu Phe His Ala Glu Gln Glu Lys Phe Leu Thr Cys Asp Glu His
                245                 250                 255
Arg Lys Lys Gln His Val Phe Leu Arg Thr Thr Gly Arg Gln Ser Ala
            260                 265                 270
Thr Ser Ala Thr Ser Ser Lys Ala Leu Trp Glu Val Glu Val Val Gln
        275                 280                 285
His Asp Pro Cys Arg Gly Gly Ala Gly Tyr Trp Asn Ser Leu Phe Arg
    290                 295                 300
Phe Lys His Leu Ala Thr Gly His Tyr Leu Ala Ala Glu Val Asp Pro
305                 310                 315                 320
Asp Phe Glu Glu Glu Cys Leu Glu Phe Gln Pro Ser Val Asp Pro Asp
                325                 330                 335
Gln Asp Ala Ser Arg Ser Arg Leu Arg Asn Ala Gln Glu Lys Met Val
            340                 345                 350
Tyr Ser Leu Val Ser Val Pro Glu Gly Asn Asp Ile Ser Ser Ile Phe
        355                 360                 365
Glu Leu Asp Pro Thr Thr Leu Arg Gly Gly Asp Ser Leu Val Pro Arg
    370                 375                 380
Asn Ser Tyr Val Arg Leu Arg His Leu Cys Thr Asn Thr Trp Val His
385                 390                 395                 400
Ser Thr Asn Ile Pro Ile Asp Lys Glu Glu Glu Lys Pro Val Met Leu
                405                 410                 415
Lys Ile Gly Thr Ser Pro Leu Lys Glu Asp Lys Glu Ala Phe Ala Ile
            420                 425                 430
Val Pro Val Ser Pro Ala Glu Val Arg Asp Leu Asp Phe Ala Asn Asp
        435                 440                 445
Ala Ser Lys Val Leu Gly Ser Ile Ala Gly Lys Leu Glu Lys Gly Thr
    450                 455                 460
Ile Thr Gln Asn Glu Arg Arg Ser Val Thr Lys Leu Leu Glu Asp Leu
465                 470                 475                 480
```

```
Val Tyr Phe Val Thr Gly Gly Thr Asn Ser Gly Gln Asp Val Leu Glu
                485                 490                 495
Val Val Phe Ser Lys Pro Asn Arg Glu Arg Gln Lys Leu Met Arg Glu
            500                 505                 510
Gln Asn Ile Leu Lys Gln Ile Phe Lys Leu Leu Gln Ala Pro Phe Thr
        515                 520                 525
Asp Cys Gly Asp Gly Pro Met Leu Arg Leu Glu Glu Leu Gly Asp Gln
    530                 535                 540
Arg His Ala Pro Phe Arg His Ile Cys Arg Leu Cys Tyr Arg Val Leu
545                 550                 555                 560
Arg His Ser Gln Gln Asp Tyr Arg Lys Asn Gln Glu Tyr Ile Ala Lys
                565                 570                 575
Gln Phe Gly Phe Met Gln Lys Gln Ile Gly Tyr Asp Val Leu Ala Glu
            580                 585                 590
Asp Thr Ile Thr Ala Leu Leu His Asn Asn Arg Lys Leu Leu Glu Lys
        595                 600                 605
His Ile Thr Ala Ala Glu Ile Asp Thr Phe Val Ser Leu Val Arg Lys
    610                 615                 620
Asn Arg Glu Pro Arg Phe Leu Asp Tyr Leu Ser Asp Leu Cys Val Ser
625                 630                 635                 640
Met Asn Lys Ser Ile Pro Val Thr Gln Glu Leu Ile Cys Lys Ala Val
                645                 650                 655
Leu Asn Pro Thr Asn Ala Asp Ile Leu Ile Glu Thr Lys Leu Val Leu
            660                 665                 670
Ser Arg Phe Glu Phe Glu Gly Val Ser Thr Gly Glu Asn Ala Leu Glu
        675                 680                 685
Ala Gly Glu Asp Glu Glu Glu Val Trp Leu Phe Trp Arg Asp Ser Asn
    690                 695                 700
Lys Glu Ile Arg Ser Lys Ser Val Arg Glu Leu Ala Gln Asp Ala Lys
705                 710                 715                 720
Glu Gly Gln Lys Glu Asp Arg Asp Val Leu Ser Tyr Tyr Arg Tyr Gln
                725                 730                 735
Leu Asn Leu Phe Ala Arg Met Cys Leu Asp Arg Gln Tyr Leu Ala Ile
            740                 745                 750
Asn Glu Ile Ser Gly Gln Leu Asp Val Asp Leu Ile Leu Arg Cys Met
        755                 760                 765
Ser Asp Glu Asn Leu Pro Tyr Asp Leu Arg Ala Ser Phe Cys Arg Leu
    770                 775                 780
Met Leu His Met His Val Asp Arg Asp Pro Gln Glu Gln Val Thr Pro
785                 790                 795                 800
Val Lys Tyr Ala Arg Leu Trp Ser Glu Ile Pro Ser Glu Ile Ala Ile
                805                 810                 815
Asp Asp Tyr Asp Ser Ser Gly Ala Ser Lys Asp Glu Ile Lys Glu Arg
            820                 825                 830
Phe Ala Gln Thr Met Glu Phe Val Glu Glu Tyr Leu Arg Asp Val Val
        835                 840                 845
Cys Gln Arg Phe Pro Phe Ser Asp Lys Glu Lys Asn Lys Leu Thr Phe
    850                 855                 860
Glu Val Val Asn Leu Ala Arg Asn Leu Ile Tyr Phe Gly Phe Tyr Asn
865                 870                 875                 880
Phe Ser Asp Leu Leu Arg Leu Thr Lys Ile Leu Leu Ala Ile Leu Asp
                885                 890                 895
Cys Val His Val Thr Thr Ile Phe Pro Ile Ser Lys Met Thr Lys Gly
            900                 905                 910
Glu Glu Asn Lys Gly Ser Asn Val Met Arg Ser Ile His Gly Val Gly
        915                 920                 925
Glu Leu Met Thr Gln Val Val Leu Arg Gly Gly Gly Phe Leu Pro Met
    930                 935                 940
Thr Pro Met Ala Ala Ala Pro Glu Gly Asn Val Lys Gln Ala Glu Pro
945                 950                 955                 960
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```
Glu Lys Glu Asp Ile Met Val Met Asp Thr Lys Leu Lys Ile Ile Glu
                965                 970                 975
Ile Leu Gln Phe Ile Leu Asn Val Arg Leu Asp Tyr Arg Ile Ser Cys
            980                 985                 990
Leu Leu Cys Ile Phe Lys Arg Glu Phe Asp Glu Ser Asn Ser Gln Ser
        995                 1000                1005
Ser Glu Thr Ser Ser Gly Asn Ser Ser Gln Glu Gly Pro Ser Asn Val
    1010                1015                1020
Pro Gly Ala Leu Asp Phe Glu His Ile Glu Glu Gln Ala Glu Gly Ile
1025                1030                1035                1040
Phe Gly Gly Ser Glu Glu Asn Thr Pro Leu Asp Leu Asp Asp His Gly
                1045                1050                1055
Gly Arg Thr Phe Leu Arg Val Leu Leu His Leu Thr Met His Asp Tyr
            1060                1065                1070
Pro Pro Leu Val Ser Gly Ala Leu Gln Leu Leu Phe Arg His Phe Ser
        1075                1080                1085
Gln Arg Gln Glu Val Leu Gln Ala Phe Lys Gln Val Gln Leu Leu Val
    1090                1095                1100
Thr Ser Gln Asp Val Asp Asn Tyr Lys Gln Ile Lys Gln Asp Leu Asp
1105                1110                1115                1120
Gln Leu Arg Ser Ile Val Glu Lys Ser Glu Leu Trp Val Tyr Lys Gly
                1125                1130                1135
Gln Gly Pro Asp Glu Pro Met Asp Gly Ala Ser Gly Glu Asn Glu His
            1140                1145                1150
Lys Lys Thr Glu Glu Gly Thr Ser Lys Pro Leu Lys His Glu Ser Thr
        1155                1160                1165
Ser Ser Tyr Asn Tyr Arg Val Val Lys Glu Ile Leu Ile Arg Leu Ser
    1170                1175                1180
Lys Leu Cys Val Gln Glu Ser Ala Ser Val Arg Lys Ser Arg Lys Gln
1185                1190                1195                1200
Gln Gln Arg Leu Leu Arg Asn Met Gly Ala His Ala Val Val Leu Glu
                1205                1210                1215
Leu Leu Gln Ile Pro Tyr Glu Lys Ala Glu Asp Thr Lys Met Gln Glu
            1220                1225                1230
Ile Met Arg Leu Ala His Glu Phe Leu Gln Asn Phe Cys Ala Gly Asn
        1235                1240                1245
Gln Gln Asn Gln Ala Leu Leu His Lys His Ile Asn Leu Phe Leu Asn
    1250                1255                1260
Pro Gly Ile Leu Glu Ala Val Thr Met Gln His Ile Phe Met Asn Asn
1265                1270                1275                1280
Phe Gln Leu Cys Ser Glu Ile Asn Glu Arg Val Val Gln His Phe Val
                1285                1290                1295
His Cys Ile Glu Thr His Gly Arg Asn Val Gln Tyr Ile Lys Phe Leu
            1300                1305                1310
Gln Thr Ile Val Lys Ala Glu Gly Lys Phe Ile Lys Lys Cys Gln Asp
        1315                1320                1325
Met Val Met Ala Glu Leu Val Asn Ser Gly Glu Asp Val Leu Val Phe
    1330                1335                1340
Tyr Asn Asp Arg Ala Ser Phe Gln Thr Leu Ile Gln Met Met Arg Ser
1345                1350                1355                1360
Glu Arg Asp Arg Met Asp Glu Asn Ser Pro Leu Phe Met Tyr His Ile
                1365                1370                1375
His Leu Val Glu Leu Leu Ala Val Cys Thr Glu Gly Lys Asn Val Tyr
            1380                1385                1390
Thr Glu Ile Lys Cys Asn Ser Leu Leu Pro Leu Asp Asp Ile Val Arg
        1395                1400                1405
Val Val Thr His Glu Asp Cys Ile Pro Glu Val Lys Ile Ala Tyr Ile
    1410                1415                1420
Asn Phe Leu Asn His Cys Tyr Val Asp Thr Glu Val Glu Met Lys Glu
1425                1430                1435                1440
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Ile Tyr Thr Ser Asn His Met Trp Lys Leu Phe Glu Asn Phe Leu Val
                1445                1450                1455
Asp Ile Cys Arg Ala Cys Asn Asn Thr Ser Asp Arg Lys His Ala Asp
            1460                1465                1470
Ser Val Leu Glu Lys Tyr Val Thr Glu Ile Val Met Ser Ile Val Thr
        1475                1480                1485
Thr Phe Phe Ser Ser Pro Phe Ser Asp Gln Ser Thr Thr Leu Gln Thr
    1490                1495                1500
Arg Gln Pro Val Phe Val Gln Leu Leu Gln Gly Val Phe Arg Val Tyr
1505                1510                1515                1520
His Cys Asn Trp Leu Met Pro Ser Gln Lys Ala Ser Val Glu Ser Cys
                1525                1530                1535
Ile Arg Val Leu Ser Asp Val Ala Lys Ser Arg Ala Ile Ala Ile Pro
            1540                1545                1550
Val Asp Leu Asp Ser Gln Val Asn Asn Leu Phe Leu Lys Ser His Asn
        1555                1560                1565
Ile Val Gln Lys Thr Ala Met Asn Trp Arg Leu Ser Ala Arg Asn Ala
    1570                1575                1580
Ala Arg Arg Asp Asp Val Leu Ala Ala Ser Arg Asp Tyr Arg Asn Ile
1585                1590                1595                1600
Ile Glu Arg Leu Gln Asp Ile Val Ser Ala Leu Glu Asp Arg Leu Arg
                1605                1610                1615
Pro Leu Val Gln Ala Glu Leu Ser Val Leu Val Asp Val Leu His Arg
            1620                1625                1630
Pro Glu Leu Leu Phe Pro Glu Asn Thr Asp Ala Arg Arg Lys Cys Glu
        1635                1640                1645
Ser Gly Gly Phe Ile Cys Lys Leu Ile Lys His Thr Lys Gln Leu Leu
    1650                1655                1660
Glu Glu Asn Glu Glu Lys Leu Cys Ile Lys Val Leu Gln Thr Leu Arg
1665                1670                1675                1680
Glu Met Met Thr Lys Asp Arg Gly Tyr Gly Glu Lys Gln Ile Ser Ile
                1685                1690                1695
Asp Glu Leu Glu Asn Ala Glu Leu Pro Gln Pro Pro Glu Ala Glu Asn
            1700                1705                1710
Ser Thr Glu Glu Leu Glu Pro Ser Pro Pro Leu Arg Gln Leu Glu Asp
        1715                1720                1725
His Lys Arg Gly Glu Ala Leu Arg Gln Ile Leu Val Asn Arg Tyr Tyr
    1730                1735                1740
Gly Asn Ile Arg Pro Ser Gly Arg Arg Glu Glu Leu Thr Ser Phe Gly
1745                1750                1755                1760
Asn Gly Pro Leu Ser Pro Gly Gly Pro Ser Lys Pro Gly Gly Gly Gly
                1765                1770                1775
Gly Gly Pro Gly Ser Gly Ser Thr Ser Arg Gly Glu Met Ser Leu Ala
            1780                1785                1790
Glu Val Gln Cys His Leu Asp Lys Glu Gly Ala Ser Asn Leu Val Ile
        1795                1800                1805
Asp Leu Ile Met Asn Ala Ser Ser Asp Arg Val Phe His Glu Ser Ile
    1810                1815                1820
Leu Leu Ala Ile Ala Leu Leu Glu Gly Gly Asn Thr Thr Ile Gln His
1825                1830                1835                1840
Ser Phe Phe Cys Arg Leu Thr Glu Asp Lys Lys Ser Glu Lys Phe Phe
                1845                1850                1855
Lys Val Phe Tyr Asp Arg Met Lys Val Ala Gln Gln Glu Ile Lys Ala
            1860                1865                1870
Thr Val Thr Val Asn Thr Ser Asp Leu Gly Asn Lys Lys Lys Asp Asp
        1875                1880                1885
Glu Val Asp Arg Asp Ala Pro Ser Arg Lys Lys Ala Lys Glu Pro Thr
    1890                1895                1900
Thr Gln Ile Thr Glu Glu Val Arg Asp Gln Leu Leu Glu Ala Ser Ala
1905                1910                1915                1920
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Ala Thr Arg Lys Ala Phe Thr Thr Phe Arg Arg Glu Ala Asp Pro Asp
                1925                1930                1935
Asp His Tyr Gln Ser Gly Glu Gly Thr Gln Ala Thr Thr Asp Lys Ala
            1940                1945                1950
Lys Asp Asp Leu Glu Met Ser Ala Val Ile Thr Ile Met Gln Pro Ile
        1955                1960                1965
Leu Arg Phe Leu Gln Leu Leu Cys Glu Asn His Asn Arg Asp Leu Gln
    1970                1975                1980
Asn Phe Leu Arg Cys Gln Asn Asn Lys Thr Asn Tyr Asn Leu Val Cys
1985                1990                1995                2000
Glu Thr Leu Gln Phe Leu Asp Cys Ile Cys Gly Ser Thr Thr Gly Gly
                2005                2010                2015
Leu Gly Leu Leu Gly Leu Tyr Ile Asn Glu Lys Asn Val Ala Leu Ile
            2020                2025                2030
Asn Gln Thr Leu Glu Ser Leu Thr Glu Tyr Cys Gln Gly Pro Cys His
        2035                2040                2045
Glu Asn Gln Asn Cys Ile Ala Thr His Glu Ser Asn Gly Ile Asp Ile
    2050                2055                2060
Ile Thr Ala Leu Ile Leu Asn Asp Ile Asn Pro Leu Gly Lys Lys Arg
2065                2070                2075                2080
Met Asp Leu Val Leu Glu Leu Lys Asn Asn Ala Ser Lys Leu Leu Leu
                2085                2090                2095
Ala Ile Met Glu Ser Arg His Asp Ser Glu Asn Ala Glu Arg Ile Leu
            2100                2105                2110
Tyr Asn Met Arg Pro Lys Glu Leu Val Glu Val Ile Lys Lys Ala Tyr
        2115                2120                2125
Met Gln Gly Glu Val Glu Phe Glu Asp Gly Glu Asn Gly Glu Asp Gly
    2130                2135                2140
Ala Ala Ser Pro Arg Asn Val Gly His Asn Ile Tyr Ile Leu Ala His
2145                2150                2155                2160
Gln Leu Ala Arg His Asn Lys Glu Leu Gln Thr Met Leu Lys Pro Gly
                2165                2170                2175
Gly Gln Val Asp Gly Asp Glu Ala Leu Glu Phe Tyr Ala Lys His Thr
            2180                2185                2190
Ala Gln Ile Glu Ile Val Arg Leu Asp Arg Thr Met Glu Gln Ile Val
        2195                2200                2205
Phe Pro Val Pro Ser Ile Cys Glu Phe Leu Thr Lys Glu Ser Lys Leu
    2210                2215                2220
Arg Ile Tyr Tyr Thr Thr Glu Arg Asp Glu Gln Gly Ser Lys Ile Asn
2225                2230                2235                2240
Asp Phe Phe Leu Arg Ser Glu Asp Leu Phe Asn Glu Met Asn Trp Gln
                2245                2250                2255
Lys Lys Leu Arg Ala Gln Pro Val Leu Tyr Trp Cys Ala Arg Asn Met
            2260                2265                2270
Ser Phe Trp Ser Ser Ile Ser Phe Asn Leu Ala Val Leu Met Asn Leu
        2275                2280                2285
Leu Val Ala Phe Phe Tyr Pro Phe Lys Gly Val Arg Gly Gly Thr Leu
    2290                2295                2300
Glu Pro His Trp Ser Gly Leu Leu Trp Thr Ala Met Leu Ile Ser Leu
2305                2310                2315                2320
Ala Ile Val Ile Ala Leu Pro Lys Pro His Gly Ile Arg Ala Leu Ile
                2325                2330                2335
Ala Ser Thr Ile Leu Arg Leu Ile Phe Ser Val Gly Leu Gln Pro Thr
            2340                2345                2350
Leu Phe Leu Leu Gly Ala Phe Asn Val Cys Asn Lys Ile Ile Phe Leu
        2355                2360                2365
Met Ser Phe Val Gly Asn Cys Gly Thr Phe Thr Arg Gly Tyr Arg Ala
    2370                2375                2380
Met Val Leu Asp Val Glu Phe Leu Tyr His Leu Leu Tyr Leu Leu Ile
2385                2390                2395                2400
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Cys Ala Met Gly Leu Phe Val His Glu Phe Phe Tyr Ser Leu Leu Leu
                2405                2410                2415
Phe Asp Leu Val Tyr Arg Glu Glu Thr Leu Leu Asn Val Ile Lys Ser
            2420                2425                2430
Val Thr Arg Asn Gly Arg Pro Ile Ile Leu Thr Ala Ala Leu Ala Leu
        2435                2440                2445
Ile Leu Val Tyr Leu Phe Ser Ile Val Gly Tyr Leu Phe Phe Lys Asp
    2450                2455                2460
Asp Phe Ile Leu Glu Val Asp Arg Leu Pro Asn Glu Thr Ala Gly Pro
2465                2470                2475                2480
Glu Thr Gly Glu Ser Leu Ala Asn Asp Phe Leu Tyr Ser Asp Val Cys
                2485                2490                2495
Arg Val Glu Thr Gly Glu Asn Cys Thr Ser Pro Ala Pro Lys Glu Glu
            2500                2505                2510
Leu Leu Pro Val Glu Glu Thr Glu Gln Asp Lys Glu His Thr Cys Glu
        2515                2520                2525
Thr Leu Leu Met Cys Ile Val Thr Val Leu Ser His Gly Leu Arg Ser
    2530                2535                2540
Gly Gly Gly Val Gly Asp Val Leu Arg Lys Pro Ser Lys Glu Glu Pro
2545                2550                2555                2560
Leu Phe Ala Ala Arg Val Ile Tyr Asp Leu Leu Phe Phe Phe Met Val
                2565                2570                2575
Ile Ile Ile Val Leu Asn Leu Ile Phe Gly Val Ile Ile Asp Thr Phe
            2580                2585                2590
Ala Asp Leu Arg Ser Glu Lys Gln Lys Lys Glu Glu Ile Leu Lys Thr
        2595                2600                2605
Thr Cys Phe Ile Cys Gly Leu Glu Arg Asp Lys Phe Asp Asn Lys Thr
    2610                2615                2620
Val Thr Phe Glu Glu His Ile Lys Glu Glu His Asn Met Trp His Tyr
2625                2630                2635                2640
Leu Cys Phe Ile Val Leu Val Lys Val Lys Asp Ser Thr Glu Tyr Thr
                2645                2650                2655
Gly Pro Glu Ser Tyr Val Ala Glu Met Ile Arg Glu Arg Asn Leu Asp
            2660                2665                2670
Trp Phe Pro Arg Met Arg Ala Met Ser Leu Val Ser Ser Asp Ser Glu
        2675                2680                2685
Gly Glu Gln Asn Glu Leu Arg Asn Leu Gln Glu Lys Leu Glu Ser Thr
    2690                2695                2700
Met Lys Leu Val Thr Asn Leu Ser Gly Gln Leu Ser Glu Leu Lys Asp
2705                2710                2715                2720
Gln Met Thr Glu Gln Arg Lys Gln Lys Gln Arg Ile Gly Leu Leu Gly
                2725                2730                2735
His Pro Pro His Met Asn Val Asn Pro Gln Gln Pro Ala
            2740                2745


<210> 15
<211> 2710
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/note =
      synthetic construct

<400> 15
Met Ser Asp Lys Met Ser Ser Phe Leu His Ile Gly Asp Ile Cys Ser
 1               5                  10                  15
Leu Tyr Ala Glu Gly Ser Thr Asn Gly Phe Ile Ser Thr Leu Gly Leu
            20                  25                  30
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Val Asp Asp Arg Cys Val Val Gln Pro Glu Ala Gly Asp Leu Asn Asn
        35                  40                  45
Pro Pro Lys Lys Phe Arg Asp Cys Leu Phe Lys Leu Cys Pro Met Asn
    50                  55                  60
Arg Tyr Ser Ala Gln Lys Gln Phe Trp Lys Ala Ala Lys Pro Gly Ala
65                  70                  75                  80
Asn Ser Thr Thr Asp Ala Val Leu Leu Asn Lys Leu His His Ala Ala
                85                  90                  95
Asp Leu Glu Lys Lys Gln Asn Glu Thr Glu Asn Arg Lys Leu Leu Gly
            100                 105                 110
Thr Val Ile Gln Tyr Gly Asn Val Ile Gln Leu Leu His Leu Lys Ser
        115                 120                 125
Asn Lys Tyr Leu Thr Val Asn Lys Arg Leu Pro Ala Leu Leu Glu Lys
    130                 135                 140
Asn Ala Met Arg Val Thr Leu Asp Glu Ala Gly Asn Glu Gly Ser Trp
145                 150                 155                 160
Phe Tyr Ile Gln Pro Phe Tyr Lys Leu Arg Ser Ile Gly Asp Ser Val
                165                 170                 175
Val Ile Gly Asp Lys Val Val Leu Asn Pro Val Asn Ala Gly Gln Pro
            180                 185                 190
Leu His Ala Ser Ser His Gln Leu Val Asp Asn Pro Gly Cys Asn Glu
        195                 200                 205
Val Asn Ser Val Asn Cys Asn Thr Ser Trp Lys Ile Val Leu Phe Met
    210                 215                 220
Lys Trp Ser Asp Asn Lys Asp Asp Ile Leu Lys Gly Gly Asp Val Val
225                 230                 235                 240
Arg Leu Phe His Ala Glu Gln Glu Lys Phe Leu Thr Cys Asp Glu His
                245                 250                 255
Arg Lys Lys Gln His Val Phe Leu Arg Thr Thr Gly Arg Gln Ser Ala
            260                 265                 270
Thr Ser Ala Thr Ser Ser Lys Ala Leu Trp Glu Val Glu Val Val Gln
        275                 280                 285
His Asp Pro Cys Arg Gly Gly Ala Gly Tyr Trp Asn Ser Leu Phe Arg
    290                 295                 300
Phe Lys His Leu Ala Thr Gly His Tyr Leu Ala Ala Glu Val Asp Pro
305                 310                 315                 320
Asp Phe Glu Glu Glu Cys Leu Glu Phe Gln Pro Ser Val Asp Pro Asp
                325                 330                 335
Gln Asp Ala Ser Arg Ser Arg Leu Arg Asn Ala Gln Glu Lys Met Val
            340                 345                 350
Tyr Ser Leu Val Ser Val Pro Glu Gly Asn Asp Ile Ser Ser Ile Phe
        355                 360                 365
Glu Leu Asp Pro Thr Thr Leu Arg Gly Gly Asp Ser Leu Val Pro Arg
    370                 375                 380
Asn Ser Tyr Val Arg Leu Arg His Leu Cys Thr Asn Thr Trp Val His
385                 390                 395                 400
Ser Thr Asn Ile Pro Ile Asp Lys Glu Glu Glu Lys Pro Val Met Leu
                405                 410                 415
Lys Ile Gly Thr Ser Pro Leu Lys Glu Asp Lys Glu Ala Phe Ala Ile
            420                 425                 430
Val Pro Val Ser Pro Ala Glu Val Arg Asp Leu Asp Phe Ala Asn Asp
        435                 440                 445
Ala Ser Lys Val Leu Gly Ser Ile Ala Gly Lys Leu Glu Lys Gly Thr
    450                 455                 460
Ile Thr Gln Asn Glu Arg Arg Ser Val Thr Lys Leu Leu Glu Asp Leu
465                 470                 475                 480
Val Tyr Phe Val Thr Gly Gly Thr Asn Ser Gly Gln Asp Val Leu Glu
                485                 490                 495
Val Val Phe Ser Lys Pro Asn Arg Glu Arg Gln Lys Leu Met Arg Glu
            500                 505                 510
```

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Gln Asn Ile Leu Lys Gln Ile Phe Lys Leu Leu Gln Ala Pro Phe Thr
        515                 520                 525
Asp Cys Gly Asp Gly Pro Met Leu Arg Leu Glu Glu Leu Gly Asp Gln
    530                 535                 540
Arg His Ala Pro Phe Arg His Ile Cys Arg Leu Cys Tyr Arg Val Leu
545                 550                 555                 560
Arg His Ser Gln Gln Asp Tyr Arg Lys Asn Gln Glu Tyr Ile Ala Lys
                565                 570                 575
Gln Phe Gly Phe Met Gln Lys Gln Ile Gly Tyr Asp Val Leu Ala Glu
            580                 585                 590
Asp Thr Ile Thr Ala Leu Leu His Asn Asn Arg Lys Leu Leu Glu Lys
        595                 600                 605
His Ile Thr Ala Ala Glu Ile Asp Thr Phe Val Ser Leu Val Arg Lys
    610                 615                 620
Asn Arg Glu Pro Arg Phe Leu Asp Tyr Leu Ser Asp Leu Cys Val Ser
625                 630                 635                 640
Met Asn Lys Ser Ile Pro Val Thr Gln Glu Leu Ile Cys Lys Ala Val
                645                 650                 655
Leu Asn Pro Thr Asn Ala Asp Ile Leu Ile Glu Thr Lys Leu Val Leu
            660                 665                 670
Ser Arg Phe Glu Phe Glu Gly Val Ser Thr Gly Glu Asn Ala Leu Glu
        675                 680                 685
Ala Gly Glu Asp Glu Glu Glu Val Trp Leu Phe Trp Arg Asp Ser Asn
    690                 695                 700
Lys Glu Ile Arg Ser Lys Ser Val Arg Glu Leu Ala Gln Asp Ala Lys
705                 710                 715                 720
Glu Gly Gln Lys Glu Asp Arg Asp Val Leu Ser Tyr Tyr Arg Tyr Gln
                725                 730                 735
Leu Asn Leu Phe Ala Arg Met Cys Leu Asp Arg Gln Tyr Leu Ala Ile
            740                 745                 750
Asn Glu Ile Ser Gly Gln Leu Asp Val Asp Leu Ile Leu Arg Cys Met
        755                 760                 765
Ser Asp Glu Asn Leu Pro Tyr Asp Leu Arg Ala Ser Phe Cys Arg Leu
    770                 775                 780
Met Leu His Met His Val Asp Arg Asp Pro Gln Glu Gln Val Thr Pro
785                 790                 795                 800
Val Lys Tyr Ala Arg Leu Trp Ser Glu Ile Pro Ser Glu Ile Ala Ile
                805                 810                 815
Asp Asp Tyr Asp Ser Ser Gly Ala Ser Lys Asp Glu Ile Lys Glu Arg
            820                 825                 830
Phe Ala Gln Thr Met Glu Phe Val Glu Glu Tyr Leu Arg Asp Val Val
        835                 840                 845
Cys Gln Arg Phe Pro Phe Ser Asp Lys Glu Lys Asn Lys Leu Thr Phe
    850                 855                 860
Glu Val Val Asn Leu Ala Arg Asn Leu Ile Tyr Phe Gly Phe Tyr Asn
865                 870                 875                 880
Phe Ser Asp Leu Leu Arg Leu Thr Lys Ile Leu Leu Ala Ile Leu Asp
                885                 890                 895
Cys Val His Val Thr Thr Ile Phe Pro Ile Ser Lys Met Thr Lys Gly
            900                 905                 910
Glu Glu Asn Lys Gly Ser Asn Val Met Arg Ser Ile His Gly Val Gly
        915                 920                 925
Glu Leu Met Thr Gln Val Val Leu Arg Gly Gly Gly Phe Leu Pro Met
    930                 935                 940
Thr Pro Met Ala Ala Ala Pro Glu Gly Asn Val Lys Gln Ala Glu Pro
945                 950                 955                 960
Glu Lys Glu Asp Ile Met Val Met Asp Thr Lys Leu Lys Ile Ile Glu
                965                 970                 975
Ile Leu Gln Phe Ile Leu Asn Val Arg Leu Asp Tyr Arg Ile Ser Cys
            980                 985                 990
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Leu Leu Cys Ile Phe Lys Arg Glu Phe Asp Glu Ser Asn Ser Gln Ser
        995                 1000                1005
Ser Glu Thr Ser Ser Gly Asn Ser Ser Gln Glu Gly Pro Ser Asn Val
    1010                1015                1020
Pro Gly Ala Leu Asp Phe Glu His Ile Glu Glu Gln Ala Glu Gly Ile
1025                1030                1035                1040
Phe Gly Gly Ser Glu Glu Asn Thr Pro Leu Asp Leu Asp Asp His Gly
                1045                1050                1055
Gly Arg Thr Phe Leu Arg Val Leu Leu His Leu Thr Met His Asp Tyr
            1060                1065                1070
Pro Pro Leu Val Ser Gly Ala Leu Gln Leu Leu Phe Arg His Phe Ser
        1075                1080                1085
Gln Arg Gln Glu Val Leu Gln Ala Phe Lys Gln Val Gln Leu Leu Val
    1090                1095                1100
Thr Ser Gln Asp Val Asp Asn Tyr Lys Gln Ile Lys Gln Asp Leu Asp
1105                1110                1115                1120
Gln Leu Arg Ser Ile Val Glu Lys Ser Glu Leu Trp Val Tyr Lys Gly
                1125                1130                1135
Gln Gly Pro Asp Glu Pro Met Asp Gly Ala Ser Gly Glu Asn Glu His
            1140                1145                1150
Lys Lys Thr Glu Glu Gly Thr Ser Lys Pro Leu Lys His Glu Ser Thr
        1155                1160                1165
Ser Ser Tyr Asn Tyr Arg Val Val Lys Glu Ile Leu Ile Arg Leu Ser
    1170                1175                1180
Lys Leu Cys Val Gln Glu Ser Ala Ser Val Arg Lys Ser Arg Lys Gln
1185                1190                1195                1200
Gln Gln Arg Leu Leu Arg Asn Met Gly Ala His Ala Val Val Leu Glu
                1205                1210                1215
Leu Leu Gln Ile Pro Tyr Glu Lys Ala Glu Asp Thr Lys Met Gln Glu
            1220                1225                1230
Ile Met Arg Leu Ala His Glu Phe Leu Gln Asn Phe Cys Ala Gly Asn
        1235                1240                1245
Gln Gln Asn Gln Ala Leu Leu His Lys His Ile Asn Leu Phe Leu Asn
    1250                1255                1260
Pro Gly Ile Leu Glu Ala Val Thr Met Gln His Ile Phe Met Asn Asn
1265                1270                1275                1280
Phe Gln Leu Cys Ser Glu Ile Asn Glu Arg Val Val Gln His Phe Val
                1285                1290                1295
His Cys Ile Glu Thr His Gly Arg Asn Val Gln Tyr Ile Lys Phe Leu
            1300                1305                1310
Gln Thr Ile Val Lys Ala Glu Gly Lys Phe Ile Lys Lys Cys Gln Asp
        1315                1320                1325
Met Val Met Ala Glu Leu Val Asn Ser Gly Glu Asp Val Leu Val Phe
    1330                1335                1340
Tyr Asn Asp Arg Ala Ser Phe Gln Thr Leu Ile Gln Met Met Arg Ser
1345                1350                1355                1360
Glu Arg Asp Arg Met Asp Glu Asn Ser Pro Leu Phe Met Tyr His Ile
                1365                1370                1375
His Leu Val Glu Leu Leu Ala Val Cys Thr Glu Gly Lys Asn Val Tyr
            1380                1385                1390
Thr Glu Ile Lys Cys Asn Ser Leu Leu Pro Leu Asp Asp Ile Val Arg
        1395                1400                1405
Val Val Thr His Glu Asp Cys Ile Pro Glu Val Lys Ile Ala Tyr Ile
    1410                1415                1420
Asn Phe Leu Asn His Cys Tyr Val Asp Thr Glu Val Glu Met Lys Glu
1425                1430                1435                1440
Ile Tyr Thr Ser Asn His Met Trp Lys Leu Phe Glu Asn Phe Leu Val
                1445                1450                1455
Asp Ile Cys Arg Ala Cys Asn Asn Thr Ser Asp Arg Lys His Ala Asp
            1460                1465                1470
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Ser Val Leu Glu Lys Tyr Val Thr Glu Ile Val Met Ser Ile Val Thr
        1475                1480                1485
Thr Phe Phe Ser Ser Pro Phe Ser Asp Gln Ser Thr Thr Leu Gln Thr
    1490                1495                1500
Arg Gln Pro Val Phe Val Gln Leu Leu Gln Gly Val Phe Arg Val Tyr
1505                1510                1515                1520
His Cys Asn Trp Leu Met Pro Ser Gln Lys Ala Ser Val Glu Ser Cys
                1525                1530                1535
Ile Arg Val Leu Ser Asp Val Ala Lys Ser Arg Ala Ile Ala Ile Pro
            1540                1545                1550
Val Asp Leu Asp Ser Gln Val Asn Asn Leu Phe Leu Lys Ser His Asn
        1555                1560                1565
Ile Val Gln Lys Thr Ala Met Asn Trp Arg Leu Ser Ala Arg Asn Ala
    1570                1575                1580
Ala Arg Arg Asp Glu Val Leu Ala Ala Ser Arg Asp Tyr Arg Asn Ile
1585                1590                1595                1600
Ile Glu Arg Leu Gln Asp Ile Val Ser Ala Leu Glu Asp Arg Leu Arg
                1605                1610                1615
Pro Leu Val Gln Ala Glu Leu Ser Val Leu Val Asp Val Leu His Arg
            1620                1625                1630
Pro Glu Leu Leu Phe Pro Glu Asn Thr Asp Ala Arg Arg Lys Cys Glu
        1635                1640                1645
Ser Gly Gly Phe Ile Cys Lys Leu Ile Lys His Thr Lys Gln Leu Leu
    1650                1655                1660
Glu Glu Asn Glu Glu Lys Leu Cys Ile Lys Val Leu Gln Thr Leu Arg
1665                1670                1675                1680
Glu Met Met Thr Lys Asp Arg Gly Tyr Gly Glu Lys Gly Glu Ala Leu
                1685                1690                1695
Arg Gln Ile Leu Val Asn Arg Tyr Tyr Gly Asn Ile Arg Pro Ser Gly
            1700                1705                1710
Arg Arg Glu Asp Leu Thr Ser Phe Gly Asn Gly Pro Leu Ser Pro Gly
        1715                1720                1725
Gly Pro Ser Lys Pro Gly Gly Gly Gly Gly Gly Pro Gly Ser Gly Ser
    1730                1735                1740
Thr Ser Arg Gly Glu Met Ser Leu Ala Glu Val Gln Cys His Leu Asp
1745                1750                1755                1760
Lys Glu Gly Ala Ser Asn Leu Val Ile Asp Leu Ile Met Asn Ala Ser
                1765                1770                1775
Ser Asp Arg Val Phe His Glu Ser Ile Leu Leu Ala Ile Ala Leu Leu
            1780                1785                1790
Glu Gly Gly Asn Thr Thr Ile Gln His Ser Phe Phe Cys Arg Leu Thr
        1795                1800                1805
Glu Asp Lys Lys Ser Glu Lys Phe Phe Lys Val Phe Tyr Asp Arg Met
    1810                1815                1820
Lys Val Ala Gln Gln Glu Ile Lys Ala Thr Val Thr Val Asn Thr Ser
1825                1830                1835                1840
Asp Leu Gly Asn Lys Lys Lys Asp Asp Glu Val Asp Arg Asp Ala Pro
                1845                1850                1855
Ser Arg Lys Lys Ala Lys Glu Pro Thr Thr Gln Ile Thr Glu Glu Val
            1860                1865                1870
Arg Asp Gln Leu Leu Glu Ala Ser Ala Ala Thr Arg Lys Ala Phe Thr
        1875                1880                1885
Thr Phe Arg Arg Glu Ala Asp Pro Asp Asp His Tyr Gln Ser Gly Glu
    1890                1895                1900
Gly Thr Gln Ala Thr Thr Asp Lys Ala Lys Asp Asp Leu Glu Met Ser
1905                1910                1915                1920
Ala Val Ile Thr Ile Met Gln Pro Ile Leu Arg Phe Leu Gln Leu Leu
                1925                1930                1935
Cys Glu Asn His Asn Arg Asp Leu Gln Asn Phe Leu Arg Cys Gln Asn
            1940                1945                1950
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Asn Lys Thr Asn Tyr Asn Leu Val Cys Glu Thr Leu Gln Phe Leu Asp
        1955                1960                1965
Cys Ile Cys Gly Ser Thr Thr Gly Gly Leu Gly Leu Leu Gly Leu Tyr
    1970                1975                1980
Ile Asn Glu Lys Asn Val Ala Leu Ile Asn Gln Thr Leu Glu Ser Leu
1985                1990                1995                2000
Thr Glu Tyr Cys Gln Gly Pro Cys His Glu Asn Gln Asn Cys Ile Ala
                2005                2010                2015
Thr His Glu Ser Asn Gly Ile Asp Ile Ile Thr Ala Leu Ile Leu Asn
            2020                2025                2030
Asp Ile Asn Pro Leu Gly Lys Lys Arg Met Asp Leu Val Leu Glu Leu
        2035                2040                2045
Lys Asn Asn Ala Ser Lys Leu Leu Leu Ala Ile Met Glu Ser Arg His
    2050                2055                2060
Asp Ser Glu Asn Ala Glu Arg Ile Leu Tyr Asn Met Arg Pro Lys Glu
2065                2070                2075                2080
Leu Val Glu Val Ile Lys Lys Ala Tyr Met Gln Gly Glu Val Glu Phe
                2085                2090                2095
Glu Asp Gly Glu Asn Gly Glu Asp Gly Ala Ala Ser Pro Arg Asn Val
            2100                2105                2110
Gly His Asn Ile Tyr Ile Leu Ala His Gln Leu Ala Arg His Asn Lys
        2115                2120                2125
Glu Leu Gln Thr Met Leu Lys Pro Gly Gly Gln Val Asp Gly Asp Glu
    2130                2135                2140
Ala Leu Glu Phe Tyr Ala Lys His Thr Ala Gln Ile Glu Ile Val Arg
2145                2150                2155                2160
Leu Asp Arg Thr Met Glu Gln Ile Val Phe Pro Val Pro Ser Ile Cys
                2165                2170                2175
Glu Phe Leu Thr Lys Glu Ser Lys Leu Arg Ile Tyr Tyr Thr Thr Glu
            2180                2185                2190
Arg Asp Glu Gln Gly Ser Lys Ile Asn Asp Phe Phe Leu Arg Ser Glu
        2195                2200                2205
Asp Leu Phe Asn Glu Met Asn Trp Gln Lys Lys Leu Arg Ala Gln Pro
    2210                2215                2220
Val Leu Tyr Trp Cys Ala Arg Asn Met Ser Phe Trp Ser Ser Ile Ser
2225                2230                2235                2240
Phe Asn Leu Ala Val Leu Met Asn Leu Leu Val Ala Phe Phe Tyr Pro
                2245                2250                2255
Phe Lys Gly Val Arg Gly Gly Thr Leu Glu Pro His Trp Ser Gly Leu
            2260                2265                2270
Leu Trp Thr Ala Met Leu Ile Ser Leu Ala Ile Val Ile Ala Leu Pro
        2275                2280                2285
Lys Pro His Gly Ile Arg Ala Leu Ile Ala Ser Thr Ile Leu Arg Leu
    2290                2295                2300
Ile Phe Ser Val Gly Leu Gln Pro Thr Leu Phe Leu Leu Gly Ala Phe
2305                2310                2315                2320
Asn Val Cys Asn Lys Ile Ile Phe Leu Met Ser Phe Val Gly Asn Cys
                2325                2330                2335
Gly Thr Phe Thr Arg Gly Tyr Arg Ala Met Val Leu Asp Val Glu Phe
            2340                2345                2350
Leu Tyr His Leu Leu Tyr Leu Leu Ile Cys Ala Met Gly Leu Phe Val
        2355                2360                2365
His Glu Phe Phe Tyr Ser Leu Leu Leu Phe Asp Leu Val Tyr Arg Glu
    2370                2375                2380
Glu Thr Leu Leu Asn Val Ile Lys Ser Val Thr Arg Asn Gly Arg Pro
2385                2390                2395                2400
Ile Ile Leu Thr Ala Ala Leu Ala Leu Ile Leu Val Tyr Leu Phe Ser
                2405                2410                2415
Ile Val Gly Tyr Leu Phe Phe Lys Asp Asp Phe Ile Leu Glu Val Asp
            2420                2425                2430
```

```
Arg Leu Pro Asn Glu Thr Ala Gly Pro Glu Thr Gly Glu Ser Leu Ala
        2435                2440                2445
Asn Asp Phe Leu Tyr Ser Asp Val Cys Arg Val Glu Thr Gly Glu Asn
    2450                2455                2460
Cys Thr Ser Pro Ala Pro Lys Glu Glu Leu Leu Pro Val Glu Glu Thr
2465                2470                2475                2480
Glu Gln Asp Lys Glu His Thr Cys Glu Thr Leu Leu Met Cys Ile Val
                2485                2490                2495
Thr Val Leu Ser His Gly Leu Arg Ser Gly Gly Gly Val Gly Asp Val
            2500                2505                2510
Leu Arg Lys Pro Ser Lys Glu Glu Pro Leu Phe Ala Ala Arg Val Ile
        2515                2520                2525
Tyr Asp Leu Leu Phe Phe Phe Met Val Ile Ile Ile Val Leu Asn Leu
    2530                2535                2540
Ile Phe Gly Val Ile Ile Asp Thr Phe Ala Asp Leu Arg Ser Glu Lys
2545                2550                2555                2560
Gln Lys Lys Glu Glu Ile Leu Lys Thr Thr Cys Phe Ile Cys Gly Leu
                2565                2570                2575
Glu Arg Asp Lys Phe Asp Asn Lys Thr Val Thr Phe Glu Glu His Ile
            2580                2585                2590
Lys Glu Glu His Asn Met Trp His Tyr Leu Cys Phe Ile Val Leu Val
        2595                2600                2605
Lys Val Lys Asp Ser Thr Glu Tyr Thr Gly Pro Glu Ser Tyr Val Ala
    2610                2615                2620
Glu Met Ile Arg Glu Arg Asn Leu Asp Trp Phe Pro Arg Met Arg Ala
2625                2630                2635                2640
Met Ser Leu Val Ser Ser Asp Ser Glu Gly Glu Gln Asn Glu Leu Arg
                2645                2650                2655
Asn Leu Gln Glu Lys Leu Glu Ser Thr Met Lys Leu Val Thr Asn Leu
            2660                2665                2670
Ser Gly Gln Leu Ser Glu Leu Lys Asp Gln Met Thr Glu Gln Arg Lys
        2675                2680                2685
Gln Lys Gln Arg Ile Gly Leu Leu Gly His Pro Pro His Met Asn Val
    2690                2695                2700
Asn Pro Gln Gln Pro Ala
2705                2710


<210> 16
<211> 2749
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/note =
      synthetic construct

<400> 16
Met Ser Asp Lys Met Ser Ser Phe Leu His Ile Gly Asp Ile Cys Ser
 1                5                  10                  15
Leu Tyr Ala Glu Gly Ser Thr Asn Gly Phe Ile Ser Thr Leu Gly Leu
            20                  25                  30
Val Asp Asp Arg Cys Val Val Gln Pro Glu Ala Gly Asp Leu Asn Asn
        35                  40                  45
Pro Pro Lys Lys Phe Arg Asp Cys Leu Phe Lys Leu Cys Pro Met Asn
    50                  55                  60
Arg Tyr Ser Ala Gln Lys Gln Phe Trp Lys Ala Ala Lys Pro Gly Ala
65                  70                  75                  80
Asn Ser Thr Thr Asp Ala Val Leu Leu Asn Lys Leu His His Ala Ala
                85                  90                  95
```

```
Asp Leu Glu Lys Lys Gln Asn Glu Thr Glu Asn Arg Lys Leu Leu Gly
            100                 105                 110
Thr Val Ile Gln Tyr Gly Asn Val Ile Gln Leu Leu His Leu Lys Ser
        115                 120                 125
Asn Lys Tyr Leu Thr Val Asn Lys Arg Leu Pro Ala Leu Leu Glu Lys
    130                 135                 140
Asn Ala Met Arg Val Thr Leu Asp Glu Ala Gly Asn Glu Gly Ser Trp
145                 150                 155                 160
Phe Tyr Ile Gln Pro Phe Tyr Lys Leu Arg Ser Ile Gly Asp Ser Val
                165                 170                 175
Val Ile Gly Asp Lys Val Val Leu Asn Pro Val Asn Ala Gly Gln Pro
            180                 185                 190
Leu His Ala Ser Ser His Gln Leu Val Asp Asn Pro Gly Cys Asn Glu
        195                 200                 205
Val Asn Ser Val Asn Cys Asn Thr Ser Trp Lys Ile Val Leu Phe Met
    210                 215                 220
Lys Trp Ser Asp Asn Lys Asp Asp Ile Leu Lys Gly Gly Asp Val Val
225                 230                 235                 240
Arg Leu Phe His Ala Glu Gln Glu Lys Phe Leu Thr Cys Asp Glu His
                245                 250                 255
Arg Lys Lys Gln His Val Phe Leu Arg Thr Thr Gly Arg Gln Ser Ala
            260                 265                 270
Thr Ser Ala Thr Ser Ser Lys Ala Leu Trp Glu Val Glu Val Val Gln
        275                 280                 285
His Asp Pro Cys Arg Gly Gly Ala Gly Tyr Trp Asn Ser Leu Phe Arg
    290                 295                 300
Phe Lys His Leu Ala Thr Gly His Tyr Leu Ala Ala Glu Val Asp Pro
305                 310                 315                 320
Asp Phe Glu Glu Glu Cys Leu Glu Phe Gln Pro Ser Val Asp Pro Asp
                325                 330                 335
Gln Asp Ala Ser Arg Ser Arg Leu Arg Asn Ala Gln Glu Lys Met Val
            340                 345                 350
Tyr Ser Leu Val Ser Val Pro Glu Gly Asn Asp Ile Ser Ser Ile Phe
        355                 360                 365
Glu Leu Asp Pro Thr Thr Leu Arg Gly Gly Asp Ser Leu Val Pro Arg
    370                 375                 380
Asn Ser Tyr Val Arg Leu Arg His Leu Cys Thr Asn Thr Trp Val His
385                 390                 395                 400
Ser Thr Asn Ile Pro Ile Asp Lys Glu Glu Glu Lys Pro Val Met Leu
                405                 410                 415
Lys Ile Gly Thr Ser Pro Leu Lys Glu Asp Lys Glu Ala Phe Ala Ile
            420                 425                 430
Val Pro Val Ser Pro Ala Glu Val Arg Asp Leu Asp Phe Ala Asn Asp
        435                 440                 445
Ala Ser Lys Val Leu Gly Ser Ile Ala Gly Lys Leu Glu Lys Gly Thr
    450                 455                 460
Ile Thr Gln Asn Glu Arg Arg Ser Val Thr Lys Leu Leu Glu Asp Leu
465                 470                 475                 480
Val Tyr Phe Val Thr Gly Gly Thr Asn Ser Gly Gln Asp Val Leu Glu
                485                 490                 495
Val Val Phe Ser Lys Pro Asn Arg Glu Arg Gln Lys Leu Met Arg Glu
            500                 505                 510
Gln Asn Ile Leu Lys Gln Ile Phe Lys Leu Leu Gln Ala Pro Phe Thr
        515                 520                 525
Asp Cys Gly Asp Gly Pro Met Leu Arg Leu Glu Glu Leu Gly Asp Gln
    530                 535                 540
Arg His Ala Pro Phe Arg His Ile Cys Arg Leu Cys Tyr Arg Val Leu
545                 550                 555                 560
Arg His Ser Gln Gln Asp Tyr Arg Lys Asn Gln Glu Tyr Ile Ala Lys
                565                 570                 575
```

```
Gln Phe Gly Phe Met Gln Lys Gln Ile Gly Tyr Asp Val Leu Ala Glu
            580                 585                 590
Asp Thr Ile Thr Ala Leu Leu His Asn Asn Arg Lys Leu Leu Glu Lys
        595                 600                 605
His Ile Thr Ala Ala Glu Ile Asp Thr Phe Val Ser Leu Val Arg Lys
    610                 615                 620
Asn Arg Glu Pro Arg Phe Leu Asp Tyr Leu Ser Asp Leu Cys Val Ser
625                 630                 635                 640
Met Asn Lys Ser Ile Pro Val Thr Gln Glu Leu Ile Cys Lys Ala Val
                645                 650                 655
Leu Asn Pro Thr Asn Ala Asp Ile Leu Ile Glu Thr Lys Leu Val Leu
            660                 665                 670
Ser Arg Phe Glu Phe Glu Gly Val Ser Thr Gly Glu Asn Ala Leu Glu
        675                 680                 685
Ala Gly Glu Asp Glu Glu Glu Val Trp Leu Phe Trp Arg Asp Ser Asn
    690                 695                 700
Lys Glu Ile Arg Ser Lys Ser Val Arg Glu Leu Ala Gln Asp Ala Lys
705                 710                 715                 720
Glu Gly Gln Lys Glu Asp Arg Asp Val Leu Ser Tyr Tyr Arg Tyr Gln
                725                 730                 735
Leu Asn Leu Phe Ala Arg Met Cys Leu Asp Arg Gln Tyr Leu Ala Ile
            740                 745                 750
Asn Glu Ile Ser Gly Gln Leu Asp Val Asp Leu Ile Leu Arg Cys Met
        755                 760                 765
Ser Asp Glu Asn Leu Pro Tyr Asp Leu Arg Ala Ser Phe Cys Arg Leu
    770                 775                 780
Met Leu His Met His Val Asp Arg Asp Pro Gln Glu Gln Val Thr Pro
785                 790                 795                 800
Val Lys Tyr Ala Arg Leu Trp Ser Glu Ile Pro Ser Glu Ile Ala Ile
                805                 810                 815
Asp Asp Tyr Asp Ser Ser Gly Ala Ser Lys Asp Glu Ile Lys Glu Arg
            820                 825                 830
Phe Ala Gln Thr Met Glu Phe Val Glu Glu Tyr Leu Arg Asp Val Val
        835                 840                 845
Cys Gln Arg Phe Pro Phe Ser Asp Lys Glu Lys Asn Lys Leu Thr Phe
    850                 855                 860
Glu Val Val Asn Leu Ala Arg Asn Leu Ile Tyr Phe Gly Phe Tyr Asn
865                 870                 875                 880
Phe Ser Asp Leu Leu Arg Leu Thr Lys Ile Leu Leu Ala Ile Leu Asp
                885                 890                 895
Cys Val His Val Thr Thr Ile Phe Pro Ile Ser Lys Met Thr Lys Gly
            900                 905                 910
Glu Glu Asn Lys Gly Ser Asn Val Met Arg Ser Ile His Gly Val Gly
        915                 920                 925
Glu Leu Met Thr Gln Val Val Leu Arg Gly Gly Gly Phe Leu Pro Met
    930                 935                 940
Thr Pro Met Ala Ala Ala Pro Glu Gly Asn Val Lys Gln Ala Glu Pro
945                 950                 955                 960
Glu Lys Glu Asp Ile Met Val Met Asp Thr Lys Leu Lys Ile Ile Glu
                965                 970                 975
Ile Leu Gln Phe Ile Leu Asn Val Arg Leu Asp Tyr Arg Ile Ser Cys
            980                 985                 990
Leu Leu Cys Ile Phe Lys Arg Glu Phe Asp Glu Ser Asn Ser Gln Ser
        995                 1000                1005
Ser Glu Thr Ser Ser Gly Asn Ser Ser Gln Glu Gly Pro Ser Asn Val
    1010                1015                1020
Pro Gly Ala Leu Asp Phe Glu His Ile Glu Glu Gln Ala Glu Gly Ile
1025                1030                1035                1040
Phe Gly Gly Ser Glu Glu Asn Thr Pro Leu Asp Leu Asp Asp His Gly
                1045                1050                1055
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Gly Arg Thr Phe Leu Arg Val Leu Leu His Leu Thr Met His Asp Tyr
            1060                1065                1070
Pro Pro Leu Val Ser Gly Ala Leu Gln Leu Leu Phe Arg His Phe Ser
        1075                1080                1085
Gln Arg Gln Glu Val Leu Gln Ala Phe Lys Gln Val Gln Leu Leu Val
    1090                1095                1100
Thr Ser Gln Asp Val Asp Asn Tyr Lys Gln Ile Lys Gln Asp Leu Asp
1105                1110                1115                1120
Gln Leu Arg Ser Ile Val Glu Lys Ser Glu Leu Trp Val Tyr Lys Gly
                1125                1130                1135
Gln Gly Pro Asp Glu Pro Met Asp Gly Ala Ser Gly Glu Asn Glu His
            1140                1145                1150
Lys Lys Thr Glu Glu Gly Thr Ser Lys Pro Leu Lys His Glu Ser Thr
        1155                1160                1165
Ser Ser Tyr Asn Tyr Arg Val Val Lys Glu Ile Leu Ile Arg Leu Ser
    1170                1175                1180
Lys Leu Cys Val Gln Glu Ser Ala Ser Val Arg Lys Ser Arg Lys Gln
1185                1190                1195                1200
Gln Gln Arg Leu Leu Arg Asn Met Gly Ala His Ala Val Val Leu Glu
                1205                1210                1215
Leu Leu Gln Ile Pro Tyr Glu Lys Ala Glu Asp Thr Lys Met Gln Glu
            1220                1225                1230
Ile Met Arg Leu Ala His Glu Phe Leu Gln Asn Phe Cys Ala Gly Asn
        1235                1240                1245
Gln Gln Asn Gln Ala Leu Leu His Lys His Ile Asn Leu Phe Leu Asn
    1250                1255                1260
Pro Gly Ile Leu Glu Ala Val Thr Met Gln His Ile Phe Met Asn Asn
1265                1270                1275                1280
Phe Gln Leu Cys Ser Glu Ile Asn Glu Arg Val Val Gln His Phe Val
                1285                1290                1295
His Cys Ile Glu Thr His Gly Arg Asn Val Gln Tyr Ile Lys Phe Leu
            1300                1305                1310
Gln Thr Ile Val Lys Ala Glu Gly Lys Phe Ile Lys Lys Cys Gln Asp
        1315                1320                1325
Met Val Met Ala Glu Leu Val Asn Ser Gly Glu Asp Val Leu Val Phe
    1330                1335                1340
Tyr Asn Asp Arg Ala Ser Phe Gln Thr Leu Ile Gln Met Met Arg Ser
1345                1350                1355                1360
Glu Arg Asp Arg Met Asp Glu Asn Ser Pro Leu Phe Met Tyr His Ile
                1365                1370                1375
His Leu Val Glu Leu Leu Ala Val Cys Thr Glu Gly Lys Asn Val Tyr
            1380                1385                1390
Thr Glu Ile Lys Cys Asn Ser Leu Leu Pro Leu Asp Asp Ile Val Arg
        1395                1400                1405
Val Val Thr His Glu Asp Cys Ile Pro Glu Val Lys Ile Ala Tyr Ile
    1410                1415                1420
Asn Phe Leu Asn His Cys Tyr Val Asp Thr Glu Val Glu Met Lys Glu
1425                1430                1435                1440
Ile Tyr Thr Ser Asn His Met Trp Lys Leu Phe Glu Asn Phe Leu Val
                1445                1450                1455
Asp Ile Cys Arg Ala Cys Asn Asn Thr Ser Asp Arg Lys His Ala Asp
            1460                1465                1470
Ser Val Leu Glu Lys Tyr Val Thr Glu Ile Val Met Ser Ile Val Thr
        1475                1480                1485
Thr Phe Phe Ser Ser Pro Phe Ser Asp Gln Ser Thr Thr Leu Gln Thr
    1490                1495                1500
Arg Gln Pro Val Phe Val Gln Leu Leu Gln Gly Val Phe Arg Val Tyr
1505                1510                1515                1520
His Cys Asn Trp Leu Met Pro Ser Gln Lys Ala Ser Val Glu Ser Cys
                1525                1530                1535
```

Ile Arg Val Leu Ser Asp Val Ala Lys Ser Arg Ala Ile Ala Ile Pro
1540 1545 1550
Val Asp Leu Asp Ser Gln Val Asn Asn Leu Phe Leu Lys Ser His Asn
1555 1560 1565
Ile Val Gln Lys Thr Ala Met Asn Trp Arg Leu Ser Ala Arg Asn Ala
1570 1575 1580
Ala Arg Arg Asp Glu Val Leu Ala Ala Ser Arg Asp Tyr Arg Asn Ile
1585 1590 1595 1600
Ile Glu Arg Leu Gln Asp Ile Val Ser Ala Leu Glu Asp Arg Leu Arg
1605 1610 1615
Pro Leu Val Gln Ala Glu Leu Ser Val Leu Val Asp Val Leu His Arg
1620 1625 1630
Pro Glu Leu Leu Phe Pro Glu Asn Thr Asp Ala Arg Arg Lys Cys Glu
1635 1640 1645
Ser Gly Gly Phe Ile Cys Lys Leu Ile Lys His Thr Lys Gln Leu Leu
1650 1655 1660
Glu Glu Asn Glu Glu Lys Leu Cys Ile Lys Val Leu Gln Thr Leu Arg
1665 1670 1675 1680
Glu Met Met Thr Lys Asp Arg Gly Tyr Gly Glu Lys Gln Ile Ser Ile
1685 1690 1695
Asp Glu Leu Glu Asn Ala Glu Leu Pro Gln Pro Pro Glu Ala Glu Asn
1700 1705 1710
Ser Thr Glu Glu Leu Glu Pro Ser Pro Pro Leu Arg Gln Leu Glu Asp
1715 1720 1725
His Lys Arg Gly Glu Ala Leu Arg Gln Ile Leu Val Asn Arg Tyr Tyr
1730 1735 1740
Gly Asn Ile Arg Pro Ser Gly Arg Arg Glu Asp Leu Thr Ser Phe Gly
1745 1750 1755 1760
Asn Gly Pro Leu Ser Pro Gly Gly Pro Ser Lys Pro Gly Gly Gly Gly
1765 1770 1775
Gly Gly Pro Gly Ser Gly Ser Thr Ser Arg Gly Glu Met Ser Leu Ala
1780 1785 1790
Glu Val Gln Cys His Leu Asp Lys Glu Gly Ala Ser Asn Leu Val Ile
1795 1800 1805
Asp Leu Ile Met Asn Ala Ser Ser Asp Arg Val Phe His Glu Ser Ile
1810 1815 1820
Leu Leu Ala Ile Ala Leu Leu Glu Gly Gly Asn Thr Thr Ile Gln His
1825 1830 1835 1840
Ser Phe Phe Cys Arg Leu Thr Glu Asp Lys Lys Ser Glu Lys Phe Phe
1845 1850 1855
Lys Val Phe Tyr Asp Arg Met Lys Val Ala Gln Gln Glu Ile Lys Ala
1860 1865 1870
Thr Val Thr Val Asn Thr Ser Asp Leu Gly Asn Lys Lys Lys Asp Asp
1875 1880 1885
Glu Val Asp Arg Asp Ala Pro Ser Arg Lys Lys Ala Lys Glu Pro Thr
1890 1895 1900
Thr Gln Ile Thr Glu Glu Val Arg Asp Gln Leu Leu Glu Ala Ser Ala
1905 1910 1915 1920
Ala Thr Arg Lys Ala Phe Thr Thr Phe Arg Arg Glu Ala Asp Pro Asp
1925 1930 1935
Asp His Tyr Gln Ser Gly Glu Gly Thr Gln Ala Thr Thr Asp Lys Ala
1940 1945 1950
Lys Asp Asp Leu Glu Met Ser Ala Val Ile Thr Ile Met Gln Pro Ile
1955 1960 1965
Leu Arg Phe Leu Gln Leu Leu Cys Glu Asn His Asn Arg Asp Leu Gln
1970 1975 1980
Asn Phe Leu Arg Cys Gln Asn Asn Lys Thr Asn Tyr Asn Leu Val Cys
1985 1990 1995 2000
Glu Thr Leu Gln Phe Leu Asp Cys Ile Cys Gly Ser Thr Thr Gly Gly
2005 2010 2015

```
Leu Gly Leu Leu Gly Leu Tyr Ile Asn Glu Lys Asn Val Ala Leu Ile
            2020                2025                2030
Asn Gln Thr Leu Glu Ser Leu Thr Glu Tyr Cys Gln Gly Pro Cys His
        2035                2040                2045
Glu Asn Gln Asn Cys Ile Ala Thr His Glu Ser Asn Gly Ile Asp Ile
    2050                2055                2060
Ile Thr Ala Leu Ile Leu Asn Asp Ile Asn Pro Leu Gly Lys Lys Arg
2065                2070                2075                2080
Met Asp Leu Val Leu Glu Leu Lys Asn Asn Ala Ser Lys Leu Leu Leu
                2085                2090                2095
Ala Ile Met Glu Ser Arg His Asp Ser Glu Asn Ala Glu Arg Ile Leu
            2100                2105                2110
Tyr Asn Met Arg Pro Lys Glu Leu Val Glu Val Ile Lys Lys Ala Tyr
        2115                2120                2125
Met Gln Gly Glu Val Glu Phe Glu Asp Gly Glu Asn Gly Glu Asp Gly
    2130                2135                2140
Ala Ala Ser Pro Arg Asn Val Gly His Asn Ile Tyr Ile Leu Ala His
2145                2150                2155                2160
Gln Leu Ala Arg His Asn Lys Glu Leu Gln Thr Met Leu Lys Pro Gly
                2165                2170                2175
Gly Gln Val Asp Gly Asp Glu Ala Leu Glu Phe Tyr Ala Lys His Thr
            2180                2185                2190
Ala Gln Ile Glu Ile Val Arg Leu Asp Arg Thr Met Glu Gln Ile Val
        2195                2200                2205
Phe Pro Val Pro Ser Ile Cys Glu Phe Leu Thr Lys Glu Ser Lys Leu
    2210                2215                2220
Arg Ile Tyr Tyr Thr Thr Glu Arg Asp Glu Gln Gly Ser Lys Ile Asn
2225                2230                2235                2240
Asp Phe Phe Leu Arg Ser Glu Asp Leu Phe Asn Glu Met Asn Trp Gln
                2245                2250                2255
Lys Lys Leu Arg Ala Gln Pro Val Leu Tyr Trp Cys Ala Arg Asn Met
            2260                2265                2270
Ser Phe Trp Ser Ser Ile Ser Phe Asn Leu Ala Val Leu Met Asn Leu
        2275                2280                2285
Leu Val Ala Phe Phe Tyr Pro Phe Lys Gly Val Arg Gly Gly Thr Leu
    2290                2295                2300
Glu Pro His Trp Ser Gly Leu Leu Trp Thr Ala Met Leu Ile Ser Leu
2305                2310                2315                2320
Ala Ile Val Ile Ala Leu Pro Lys Pro His Gly Ile Arg Ala Leu Ile
                2325                2330                2335
Ala Ser Thr Ile Leu Arg Leu Ile Phe Ser Val Gly Leu Gln Pro Thr
            2340                2345                2350
Leu Phe Leu Leu Gly Ala Phe Asn Val Cys Asn Lys Ile Ile Phe Leu
        2355                2360                2365
Met Ser Phe Val Gly Asn Cys Gly Thr Phe Thr Arg Gly Tyr Arg Ala
    2370                2375                2380
Met Val Leu Asp Val Glu Phe Leu Tyr His Leu Leu Tyr Leu Leu Ile
2385                2390                2395                2400
Cys Ala Met Gly Leu Phe Val His Glu Phe Phe Tyr Ser Leu Leu Leu
                2405                2410                2415
Phe Asp Leu Val Tyr Arg Glu Glu Thr Leu Leu Asn Val Ile Lys Ser
            2420                2425                2430
Val Thr Arg Asn Gly Arg Pro Ile Ile Leu Thr Ala Ala Leu Ala Leu
        2435                2440                2445
Ile Leu Val Tyr Leu Phe Ser Ile Val Gly Tyr Leu Phe Phe Lys Asp
    2450                2455                2460
Asp Phe Ile Leu Glu Val Asp Arg Leu Pro Asn Glu Thr Ala Gly Pro
2465                2470                2475                2480
Glu Thr Gly Glu Ser Leu Ala Asn Asp Phe Leu Tyr Ser Asp Val Cys
                2485                2490                2495
```

```
Arg Val Glu Thr Gly Glu Asn Cys Thr Ser Pro Ala Pro Lys Glu Glu
            2500                2505                2510
Leu Leu Pro Val Glu Glu Thr Glu Gln Asp Lys Glu His Thr Cys Glu
        2515                2520                2525
Thr Leu Leu Met Cys Ile Val Thr Val Leu Ser His Gly Leu Arg Ser
    2530                2535                2540
Gly Gly Gly Val Gly Asp Val Leu Arg Lys Pro Ser Lys Glu Glu Pro
2545                2550                2555                2560
Leu Phe Ala Ala Arg Val Ile Tyr Asp Leu Leu Phe Phe Phe Met Val
                2565                2570                2575
Ile Ile Ile Val Leu Asn Leu Ile Phe Gly Val Ile Ile Asp Thr Phe
            2580                2585                2590
Ala Asp Leu Arg Ser Glu Lys Gln Lys Lys Glu Glu Ile Leu Lys Thr
        2595                2600                2605
Thr Cys Phe Ile Cys Gly Leu Glu Arg Asp Lys Phe Asp Asn Lys Thr
    2610                2615                2620
Val Thr Phe Glu Glu His Ile Lys Glu Glu His Asn Met Trp His Tyr
2625                2630                2635                2640
Leu Cys Phe Ile Val Leu Val Lys Val Lys Asp Ser Thr Glu Tyr Thr
                2645                2650                2655
Gly Pro Glu Ser Tyr Val Ala Glu Met Ile Arg Glu Arg Asn Leu Asp
            2660                2665                2670
Trp Phe Pro Arg Met Arg Ala Met Ser Leu Val Ser Ser Asp Ser Glu
        2675                2680                2685
Gly Glu Gln Asn Glu Leu Arg Asn Leu Gln Glu Lys Leu Glu Ser Thr
    2690                2695                2700
Met Lys Leu Val Thr Asn Leu Ser Gly Gln Leu Ser Glu Leu Lys Asp
2705                2710                2715                2720
Gln Met Thr Glu Gln Arg Lys Gln Lys Gln Arg Ile Gly Leu Leu Gly
                2725                2730                2735
His Pro Pro His Met Asn Val Asn Pro Gln Gln Pro Ala
            2740                2745
```

<210> 17
<211> 2710
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/note =
synthetic construct

<400> 17

```
Met Ser Asp Lys Met Ser Ser Phe Leu His Ile Gly Asp Ile Cys Ser
 1               5                  10                  15
Leu Tyr Ala Glu Gly Ser Thr Asn Gly Phe Ile Ser Thr Leu Gly Leu
            20                  25                  30
Val Asp Asp Arg Cys Val Val Gln Pro Glu Ala Gly Asp Leu Asn Asn
        35                  40                  45
Pro Pro Lys Lys Phe Arg Asp Cys Leu Phe Lys Leu Cys Pro Met Asn
    50                  55                  60
Arg Tyr Ser Ala Gln Lys Gln Phe Trp Lys Ala Ala Lys Pro Gly Ala
65                  70                  75                  80
Asn Ser Thr Thr Asp Ala Val Leu Leu Asn Lys Leu His His Ala Ala
                85                  90                  95
Asp Leu Glu Lys Lys Gln Asn Glu Thr Glu Asn Arg Lys Leu Leu Gly
            100                 105                 110
Thr Val Ile Gln Tyr Gly Asn Val Ile Gln Leu Leu His Leu Lys Ser
        115                 120                 125
```

```
Asn Lys Tyr Leu Thr Val Asn Lys Arg Leu Pro Ala Leu Leu Glu Lys
    130                 135                 140
Asn Ala Met Arg Val Thr Leu Asp Glu Ala Gly Asn Glu Gly Ser Trp
145                 150                 155                 160
Phe Tyr Ile Gln Pro Phe Tyr Lys Leu Arg Ser Ile Gly Asp Ser Val
                165                 170                 175
Val Ile Gly Asp Lys Val Val Leu Asn Pro Val Asn Ala Gly Gln Pro
            180                 185                 190
Leu His Ala Ser Ser His Gln Leu Val Asp Asn Pro Gly Cys Asn Glu
        195                 200                 205
Val Asn Ser Val Asn Cys Asn Thr Ser Trp Lys Ile Val Leu Phe Met
    210                 215                 220
Lys Trp Ser Asp Asn Lys Asp Asp Ile Leu Lys Gly Gly Asp Val Val
225                 230                 235                 240
Arg Leu Phe His Ala Glu Gln Glu Lys Phe Leu Thr Cys Asp Glu His
                245                 250                 255
Arg Lys Lys Gln His Val Phe Leu Arg Thr Thr Gly Arg Gln Ser Ala
            260                 265                 270
Thr Ser Ala Thr Ser Ser Lys Ala Leu Trp Glu Val Glu Val Val Gln
        275                 280                 285
His Asp Pro Cys Arg Gly Gly Ala Gly Tyr Trp Asn Ser Leu Phe Arg
    290                 295                 300
Phe Lys His Leu Ala Thr Gly His Tyr Leu Ala Ala Glu Val Asp Pro
305                 310                 315                 320
Asp Phe Glu Glu Glu Cys Leu Glu Phe Gln Pro Ser Val Asp Pro Asp
                325                 330                 335
Gln Asp Ala Ser Arg Ser Arg Leu Arg Asn Ala Gln Glu Lys Met Val
            340                 345                 350
Tyr Ser Leu Val Ser Val Pro Glu Gly Asn Asp Ile Ser Ser Ile Phe
        355                 360                 365
Glu Leu Asp Pro Thr Thr Leu Arg Gly Gly Asp Ser Leu Val Pro Arg
    370                 375                 380
Asn Ser Tyr Val Arg Leu Arg His Leu Cys Thr Asn Thr Trp Val His
385                 390                 395                 400
Ser Thr Asn Ile Pro Ile Asp Lys Glu Glu Glu Lys Pro Val Met Leu
                405                 410                 415
Lys Ile Gly Thr Ser Pro Leu Lys Glu Asp Lys Glu Ala Phe Ala Ile
            420                 425                 430
Val Pro Val Ser Pro Ala Glu Val Arg Asp Leu Asp Phe Ala Asn Asp
        435                 440                 445
Ala Ser Lys Val Leu Gly Ser Ile Ala Gly Lys Leu Glu Lys Gly Thr
    450                 455                 460
Ile Thr Gln Asn Glu Arg Arg Ser Val Thr Lys Leu Leu Glu Asp Leu
465                 470                 475                 480
Val Tyr Phe Val Thr Gly Gly Thr Asn Ser Gly Gln Asp Val Leu Glu
                485                 490                 495
Val Val Phe Ser Lys Pro Asn Arg Glu Arg Gln Lys Leu Met Arg Glu
            500                 505                 510
Gln Asn Ile Leu Lys Gln Ile Phe Lys Leu Leu Gln Ala Pro Phe Thr
        515                 520                 525
Asp Cys Gly Asp Gly Pro Met Leu Arg Leu Glu Glu Leu Gly Asp Gln
    530                 535                 540
Arg His Ala Pro Phe Arg His Ile Cys Arg Leu Cys Tyr Arg Val Leu
545                 550                 555                 560
Arg His Ser Gln Gln Asp Tyr Arg Lys Asn Gln Glu Tyr Ile Ala Lys
                565                 570                 575
Gln Phe Gly Phe Met Gln Lys Gln Ile Gly Tyr Asp Val Leu Ala Glu
            580                 585                 590
Asp Thr Ile Thr Ala Leu Leu His Asn Asn Arg Lys Leu Leu Glu Lys
        595                 600                 605
```

```
His Ile Thr Ala Ala Glu Ile Asp Thr Phe Val Ser Leu Val Arg Lys
    610                 615                 620
Asn Arg Glu Pro Arg Phe Leu Asp Tyr Leu Ser Asp Leu Cys Val Ser
625                 630                 635                 640
Met Asn Lys Ser Ile Pro Val Thr Gln Glu Leu Ile Cys Lys Ala Val
                645                 650                 655
Leu Asn Pro Thr Asn Ala Asp Ile Leu Ile Glu Thr Lys Leu Val Leu
            660                 665                 670
Ser Arg Phe Glu Phe Glu Gly Val Ser Thr Gly Glu Asn Ala Leu Glu
        675                 680                 685
Ala Gly Glu Asp Glu Glu Glu Val Trp Leu Phe Trp Arg Asp Ser Asn
    690                 695                 700
Lys Glu Ile Arg Ser Lys Ser Val Arg Glu Leu Ala Gln Asp Ala Lys
705                 710                 715                 720
Glu Gly Gln Lys Glu Asp Arg Asp Val Leu Ser Tyr Tyr Arg Tyr Gln
                725                 730                 735
Leu Asn Leu Phe Ala Arg Met Cys Leu Asp Arg Gln Tyr Leu Ala Ile
            740                 745                 750
Asn Glu Ile Ser Gly Gln Leu Asp Val Asp Leu Ile Leu Arg Cys Met
        755                 760                 765
Ser Asp Glu Asn Leu Pro Tyr Asp Leu Arg Ala Ser Phe Cys Arg Leu
    770                 775                 780
Met Leu His Met His Val Asp Arg Asp Pro Gln Glu Gln Val Thr Pro
785                 790                 795                 800
Val Lys Tyr Ala Arg Leu Trp Ser Glu Ile Pro Ser Glu Ile Ala Ile
                805                 810                 815
Asp Asp Tyr Asp Ser Ser Gly Ala Ser Lys Asp Glu Ile Lys Glu Arg
            820                 825                 830
Phe Ala Gln Thr Met Glu Phe Val Glu Glu Tyr Leu Arg Asp Val Val
        835                 840                 845
Cys Gln Arg Phe Pro Phe Ser Asp Lys Glu Lys Asn Lys Leu Thr Phe
    850                 855                 860
Glu Val Val Asn Leu Ala Arg Asn Leu Ile Tyr Phe Gly Phe Tyr Asn
865                 870                 875                 880
Phe Ser Asp Leu Leu Arg Leu Thr Lys Ile Leu Leu Ala Ile Leu Asp
                885                 890                 895
Cys Val His Val Thr Thr Ile Phe Pro Ile Ser Lys Met Thr Lys Gly
            900                 905                 910
Glu Glu Asn Lys Gly Ser Asn Val Met Arg Ser Ile His Gly Val Gly
        915                 920                 925
Glu Leu Met Thr Gln Val Val Leu Arg Gly Gly Gly Phe Leu Pro Met
    930                 935                 940
Thr Pro Met Ala Ala Ala Pro Glu Gly Asn Val Lys Gln Ala Glu Pro
945                 950                 955                 960
Glu Lys Glu Asp Ile Met Val Met Asp Thr Lys Leu Lys Ile Ile Glu
                965                 970                 975
Ile Leu Gln Phe Ile Leu Asn Val Arg Leu Asp Tyr Arg Ile Ser Cys
            980                 985                 990
Leu Leu Cys Ile Phe Lys Arg Glu Phe Asp Glu Ser Asn Ser Gln Ser
        995                 1000                1005
Ser Glu Thr Ser Ser Gly Asn Ser Ser Gln Glu Gly Pro Ser Asn Val
    1010                1015                1020
Pro Gly Ala Leu Asp Phe Glu His Ile Glu Glu Gln Ala Glu Gly Ile
1025                1030                1035                1040
Phe Gly Gly Ser Glu Glu Asn Thr Pro Leu Asp Leu Asp Asp His Gly
                1045                1050                1055
Gly Arg Thr Phe Leu Arg Val Leu Leu His Leu Thr Met His Asp Tyr
            1060                1065                1070
Pro Pro Leu Val Ser Gly Ala Leu Gln Leu Leu Phe Arg His Phe Ser
        1075                1080                1085
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Gln Arg Gln Glu Val Leu Gln Ala Phe Lys Gln Val Gln Leu Leu Val
    1090                1095                1100
Thr Ser Gln Asp Val Asp Asn Tyr Lys Gln Ile Lys Gln Asp Leu Asp
1105                1110                1115                1120
Gln Leu Arg Ser Ile Val Glu Lys Ser Glu Leu Trp Val Tyr Lys Gly
                1125                1130                1135
Gln Gly Pro Asp Glu Pro Met Asp Gly Ala Ser Gly Glu Asn Glu His
            1140                1145                1150
Lys Lys Thr Glu Glu Gly Thr Ser Lys Pro Leu Lys His Glu Ser Thr
        1155                1160                1165
Ser Ser Tyr Asn Tyr Arg Val Val Lys Glu Ile Leu Ile Arg Leu Ser
    1170                1175                1180
Lys Leu Cys Val Gln Glu Ser Ala Ser Val Arg Lys Ser Arg Lys Gln
1185                1190                1195                1200
Gln Gln Arg Leu Leu Arg Asn Met Gly Ala His Ala Val Val Leu Glu
                1205                1210                1215
Leu Leu Gln Ile Pro Tyr Glu Lys Ala Glu Asp Thr Lys Met Gln Glu
            1220                1225                1230
Ile Met Arg Leu Ala His Glu Phe Leu Gln Asn Phe Cys Ala Gly Asn
        1235                1240                1245
Gln Gln Asn Gln Ala Leu Leu His Lys His Ile Asn Leu Phe Leu Asn
    1250                1255                1260
Pro Gly Ile Leu Glu Ala Val Thr Met Gln His Ile Phe Met Asn Asn
1265                1270                1275                1280
Phe Gln Leu Cys Ser Glu Ile Asn Glu Arg Val Val Gln His Phe Val
                1285                1290                1295
His Cys Ile Glu Thr His Gly Arg Asn Val Gln Tyr Ile Lys Phe Leu
            1300                1305                1310
Gln Thr Ile Val Lys Ala Glu Gly Lys Phe Ile Lys Lys Cys Gln Asp
        1315                1320                1325
Met Val Met Ala Glu Leu Val Asn Ser Gly Glu Asp Val Leu Val Phe
    1330                1335                1340
Tyr Asn Asp Arg Ala Ser Phe Gln Thr Leu Ile Gln Met Met Arg Ser
1345                1350                1355                1360
Glu Arg Asp Arg Met Asp Glu Asn Ser Pro Leu Phe Met Tyr His Ile
                1365                1370                1375
His Leu Val Glu Leu Leu Ala Val Cys Thr Glu Gly Lys Asn Val Tyr
            1380                1385                1390
Thr Glu Ile Lys Cys Asn Ser Leu Leu Pro Leu Asp Asp Ile Val Arg
        1395                1400                1405
Val Val Thr His Glu Asp Cys Ile Pro Glu Val Lys Ile Ala Tyr Ile
    1410                1415                1420
Asn Phe Leu Asn His Cys Tyr Val Asp Thr Glu Val Glu Met Lys Glu
1425                1430                1435                1440
Ile Tyr Thr Ser Asn His Met Trp Lys Leu Phe Glu Asn Phe Leu Val
                1445                1450                1455
Asp Ile Cys Arg Ala Cys Asn Asn Thr Ser Asp Arg Lys His Ala Asp
            1460                1465                1470
Ser Val Leu Glu Lys Tyr Val Thr Glu Ile Val Met Ser Ile Val Thr
        1475                1480                1485
Thr Phe Phe Ser Ser Pro Phe Ser Asp Gln Ser Thr Thr Leu Gln Thr
    1490                1495                1500
Arg Gln Pro Val Phe Val Gln Leu Leu Gln Gly Val Phe Arg Val Tyr
1505                1510                1515                1520
His Cys Asn Trp Leu Met Pro Ser Gln Lys Ala Ser Val Glu Ser Cys
                1525                1530                1535
Ile Arg Val Leu Ser Asp Val Ala Lys Ser Arg Ala Ile Ala Ile Pro
            1540                1545                1550
Val Asp Leu Asp Ser Gln Val Asn Asn Leu Phe Leu Lys Ser His Asn
        1555                1560                1565
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Ile Val Gln Lys Thr Ala Met Asn Trp Arg Leu Ser Ala Arg Asn Ala
    1570                1575                1580
Ala Arg Arg Asp Ser Val Leu Ala Ala Ser Arg Asp Tyr Arg Asn Ile
1585                1590                1595                1600
Ile Glu Arg Leu Gln Asp Ile Val Ser Ala Leu Glu Asp Arg Leu Arg
                1605                1610                1615
Pro Leu Val Gln Ala Glu Leu Ser Val Leu Val Asp Val Leu His Arg
            1620                1625                1630
Pro Glu Leu Leu Phe Pro Glu Asn Thr Asp Ala Arg Arg Lys Cys Glu
        1635                1640                1645
Ser Gly Gly Phe Ile Cys Lys Leu Ile Lys His Thr Lys Gln Leu Leu
    1650                1655                1660
Glu Glu Asn Glu Glu Lys Leu Cys Ile Lys Val Leu Gln Thr Leu Arg
1665                1670                1675                1680
Glu Met Met Thr Lys Asp Arg Gly Tyr Gly Glu Lys Gly Glu Ala Leu
                1685                1690                1695
Arg Gln Ile Leu Val Asn Arg Tyr Tyr Gly Asn Ile Arg Pro Ser Gly
            1700                1705                1710
Arg Arg Glu Ser Leu Thr Ser Phe Gly Asn Gly Pro Leu Ser Pro Gly
        1715                1720                1725
Gly Pro Ser Lys Pro Gly Gly Gly Gly Gly Gly Pro Gly Ser Gly Ser
    1730                1735                1740
Thr Ser Arg Gly Glu Met Ser Leu Ala Glu Val Gln Cys His Leu Asp
1745                1750                1755                1760
Lys Glu Gly Ala Ser Asn Leu Val Ile Asp Leu Ile Met Asn Ala Ser
                1765                1770                1775
Ser Asp Arg Val Phe His Glu Ser Ile Leu Leu Ala Ile Ala Leu Leu
            1780                1785                1790
Glu Gly Gly Asn Thr Thr Ile Gln His Ser Phe Phe Cys Arg Leu Thr
        1795                1800                1805
Glu Asp Lys Lys Ser Glu Lys Phe Phe Lys Val Phe Tyr Asp Arg Met
    1810                1815                1820
Lys Val Ala Gln Gln Glu Ile Lys Ala Thr Val Thr Val Asn Thr Ser
1825                1830                1835                1840
Asp Leu Gly Asn Lys Lys Lys Asp Asp Glu Val Asp Arg Asp Ala Pro
                1845                1850                1855
Ser Arg Lys Lys Ala Lys Glu Pro Thr Thr Gln Ile Thr Glu Glu Val
            1860                1865                1870
Arg Asp Gln Leu Leu Glu Ala Ser Ala Ala Thr Arg Lys Ala Phe Thr
        1875                1880                1885
Thr Phe Arg Arg Glu Ala Asp Pro Asp Asp His Tyr Gln Ser Gly Glu
    1890                1895                1900
Gly Thr Gln Ala Thr Thr Asp Lys Ala Lys Asp Asp Leu Glu Met Ser
1905                1910                1915                1920
Ala Val Ile Thr Ile Met Gln Pro Ile Leu Arg Phe Leu Gln Leu Leu
                1925                1930                1935
Cys Glu Asn His Asn Arg Asp Leu Gln Asn Phe Leu Arg Cys Gln Asn
            1940                1945                1950
Asn Lys Thr Asn Tyr Asn Leu Val Cys Glu Thr Leu Gln Phe Leu Asp
        1955                1960                1965
Cys Ile Cys Gly Ser Thr Thr Gly Gly Leu Gly Leu Leu Gly Leu Tyr
    1970                1975                1980
Ile Asn Glu Lys Asn Val Ala Leu Ile Asn Gln Thr Leu Glu Ser Leu
1985                1990                1995                2000
Thr Glu Tyr Cys Gln Gly Pro Cys His Glu Asn Gln Asn Cys Ile Ala
                2005                2010                2015
Thr His Glu Ser Asn Gly Ile Asp Ile Ile Thr Ala Leu Ile Leu Asn
            2020                2025                2030
Asp Ile Asn Pro Leu Gly Lys Lys Arg Met Asp Leu Val Leu Glu Leu
        2035                2040                2045
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Lys Asn Asn Ala Ser Lys Leu Leu Leu Ala Ile Met Glu Ser Arg His
2050 2055 2060
Asp Ser Glu Asn Ala Glu Arg Ile Leu Tyr Asn Met Arg Pro Lys Glu
2065 2070 2075 2080
Leu Val Glu Val Ile Lys Lys Ala Tyr Met Gln Gly Glu Val Glu Phe
2085 2090 2095
Glu Asp Gly Glu Asn Gly Glu Asp Gly Ala Ala Ser Pro Arg Asn Val
2100 2105 2110
Gly His Asn Ile Tyr Ile Leu Ala His Gln Leu Ala Arg His Asn Lys
2115 2120 2125
Glu Leu Gln Thr Met Leu Lys Pro Gly Gly Gln Val Asp Gly Asp Glu
2130 2135 2140
Ala Leu Glu Phe Tyr Ala Lys His Thr Ala Gln Ile Glu Ile Val Arg
2145 2150 2155 2160
Leu Asp Arg Thr Met Glu Gln Ile Val Phe Pro Val Pro Ser Ile Cys
2165 2170 2175
Glu Phe Leu Thr Lys Glu Ser Lys Leu Arg Ile Tyr Tyr Thr Thr Glu
2180 2185 2190
Arg Asp Glu Gln Gly Ser Lys Ile Asn Asp Phe Phe Leu Arg Ser Glu
2195 2200 2205
Asp Leu Phe Asn Glu Met Asn Trp Gln Lys Lys Leu Arg Ala Gln Pro
2210 2215 2220
Val Leu Tyr Trp Cys Ala Arg Asn Met Ser Phe Trp Ser Ser Ile Ser
2225 2230 2235 2240
Phe Asn Leu Ala Val Leu Met Asn Leu Leu Val Ala Phe Phe Tyr Pro
2245 2250 2255
Phe Lys Gly Val Arg Gly Gly Thr Leu Glu Pro His Trp Ser Gly Leu
2260 2265 2270
Leu Trp Thr Ala Met Leu Ile Ser Leu Ala Ile Val Ile Ala Leu Pro
2275 2280 2285
Lys Pro His Gly Ile Arg Ala Leu Ile Ala Ser Thr Ile Leu Arg Leu
2290 2295 2300
Ile Phe Ser Val Gly Leu Gln Pro Thr Leu Phe Leu Leu Gly Ala Phe
2305 2310 2315 2320
Asn Val Cys Asn Lys Ile Ile Phe Leu Met Ser Phe Val Gly Asn Cys
2325 2330 2335
Gly Thr Phe Thr Arg Gly Tyr Arg Ala Met Val Leu Asp Val Glu Phe
2340 2345 2350
Leu Tyr His Leu Leu Tyr Leu Leu Ile Cys Ala Met Gly Leu Phe Val
2355 2360 2365
His Glu Phe Phe Tyr Ser Leu Leu Leu Phe Asp Leu Val Tyr Arg Glu
2370 2375 2380
Glu Thr Leu Leu Asn Val Ile Lys Ser Val Thr Arg Asn Gly Arg Pro
2385 2390 2395 2400
Ile Ile Leu Thr Ala Ala Leu Ala Leu Ile Leu Val Tyr Leu Phe Ser
2405 2410 2415
Ile Val Gly Tyr Leu Phe Phe Lys Asp Asp Phe Ile Leu Glu Val Asp
2420 2425 2430
Arg Leu Pro Asn Glu Thr Ala Gly Pro Glu Thr Gly Glu Ser Leu Ala
2435 2440 2445
Asn Asp Phe Leu Tyr Ser Asp Val Cys Arg Val Glu Thr Gly Glu Asn
2450 2455 2460
Cys Thr Ser Pro Ala Pro Lys Glu Glu Leu Leu Pro Val Glu Glu Thr
2465 2470 2475 2480
Glu Gln Asp Lys Glu His Thr Cys Glu Thr Leu Leu Met Cys Ile Val
2485 2490 2495
Thr Val Leu Ser His Gly Leu Arg Ser Gly Gly Gly Val Gly Asp Val
2500 2505 2510
Leu Arg Lys Pro Ser Lys Glu Glu Pro Leu Phe Ala Ala Arg Val Ile
2515 2520 2525

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Tyr Asp Leu Leu Phe Phe Phe Met Val Ile Ile Ile Val Leu Asn Leu
    2530                2535                2540
Ile Phe Gly Val Ile Ile Asp Thr Phe Ala Asp Leu Arg Ser Glu Lys
2545                2550                2555                2560
Gln Lys Lys Glu Glu Ile Leu Lys Thr Thr Cys Phe Ile Cys Gly Leu
                2565                2570                2575
Glu Arg Asp Lys Phe Asp Asn Lys Thr Val Thr Phe Glu Glu His Ile
            2580                2585                2590
Lys Glu Glu His Asn Met Trp His Tyr Leu Cys Phe Ile Val Leu Val
        2595                2600                2605
Lys Val Lys Asp Ser Thr Glu Tyr Thr Gly Pro Glu Ser Tyr Val Ala
    2610                2615                2620
Glu Met Ile Arg Glu Arg Asn Leu Asp Trp Phe Pro Arg Met Arg Ala
2625                2630                2635                2640
Met Ser Leu Val Ser Ser Asp Ser Glu Gly Glu Gln Asn Glu Leu Arg
                2645                2650                2655
Asn Leu Gln Glu Lys Leu Glu Ser Thr Met Lys Leu Val Thr Asn Leu
            2660                2665                2670
Ser Gly Gln Leu Ser Glu Leu Lys Asp Gln Met Thr Glu Gln Arg Lys
        2675                2680                2685
Gln Lys Gln Arg Ile Gly Leu Leu Gly His Pro Pro His Met Asn Val
    2690                2695                2700
Asn Pro Gln Gln Pro Ala
2705                2710


<210> 18
<211> 2749
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/note =
      synthetic construct

<400> 18
Met Ser Asp Lys Met Ser Ser Phe Leu His Ile Gly Asp Ile Cys Ser
 1                5                  10                  15
Leu Tyr Ala Glu Gly Ser Thr Asn Gly Phe Ile Ser Thr Leu Gly Leu
            20                  25                  30
Val Asp Asp Arg Cys Val Val Gln Pro Glu Ala Gly Asp Leu Asn Asn
        35                  40                  45
Pro Pro Lys Lys Phe Arg Asp Cys Leu Phe Lys Leu Cys Pro Met Asn
    50                  55                  60
Arg Tyr Ser Ala Gln Lys Gln Phe Trp Lys Ala Ala Lys Pro Gly Ala
65                  70                  75                  80
Asn Ser Thr Thr Asp Ala Val Leu Leu Asn Lys Leu His His Ala Ala
                85                  90                  95
Asp Leu Glu Lys Lys Gln Asn Glu Thr Glu Asn Arg Lys Leu Leu Gly
            100                 105                 110
Thr Val Ile Gln Tyr Gly Asn Val Ile Gln Leu Leu His Leu Lys Ser
        115                 120                 125
Asn Lys Tyr Leu Thr Val Asn Lys Arg Leu Pro Ala Leu Leu Glu Lys
    130                 135                 140
Asn Ala Met Arg Val Thr Leu Asp Glu Ala Gly Asn Glu Gly Ser Trp
145                 150                 155                 160
Phe Tyr Ile Gln Pro Phe Tyr Lys Leu Arg Ser Ile Gly Asp Ser Val
                165                 170                 175
Val Ile Gly Asp Lys Val Val Leu Asn Pro Val Asn Ala Gly Gln Pro
            180                 185                 190
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Leu His Ala Ser Ser His Gln Leu Val Asp Asn Pro Gly Cys Asn Glu
        195                 200                 205
Val Asn Ser Val Asn Cys Asn Thr Ser Trp Lys Ile Val Leu Phe Met
    210                 215                 220
Lys Trp Ser Asp Asn Lys Asp Asp Ile Leu Lys Gly Gly Asp Val Val
225                 230                 235                 240
Arg Leu Phe His Ala Glu Gln Glu Lys Phe Leu Thr Cys Asp Glu His
                245                 250                 255
Arg Lys Lys Gln His Val Phe Leu Arg Thr Thr Gly Arg Gln Ser Ala
            260                 265                 270
Thr Ser Ala Thr Ser Ser Lys Ala Leu Trp Glu Val Glu Val Val Gln
        275                 280                 285
His Asp Pro Cys Arg Gly Gly Ala Gly Tyr Trp Asn Ser Leu Phe Arg
    290                 295                 300
Phe Lys His Leu Ala Thr Gly His Tyr Leu Ala Ala Glu Val Asp Pro
305                 310                 315                 320
Asp Phe Glu Glu Glu Cys Leu Glu Phe Gln Pro Ser Val Asp Pro Asp
                325                 330                 335
Gln Asp Ala Ser Arg Ser Arg Leu Arg Asn Ala Gln Glu Lys Met Val
            340                 345                 350
Tyr Ser Leu Val Ser Val Pro Glu Gly Asn Asp Ile Ser Ser Ile Phe
        355                 360                 365
Glu Leu Asp Pro Thr Thr Leu Arg Gly Gly Asp Ser Leu Val Pro Arg
    370                 375                 380
Asn Ser Tyr Val Arg Leu Arg His Leu Cys Thr Asn Thr Trp Val His
385                 390                 395                 400
Ser Thr Asn Ile Pro Ile Asp Lys Glu Glu Glu Lys Pro Val Met Leu
                405                 410                 415
Lys Ile Gly Thr Ser Pro Leu Lys Glu Asp Lys Glu Ala Phe Ala Ile
            420                 425                 430
Val Pro Val Ser Pro Ala Glu Val Arg Asp Leu Asp Phe Ala Asn Asp
        435                 440                 445
Ala Ser Lys Val Leu Gly Ser Ile Ala Gly Lys Leu Glu Lys Gly Thr
    450                 455                 460
Ile Thr Gln Asn Glu Arg Arg Ser Val Thr Lys Leu Leu Glu Asp Leu
465                 470                 475                 480
Val Tyr Phe Val Thr Gly Gly Thr Asn Ser Gly Gln Asp Val Leu Glu
                485                 490                 495
Val Val Phe Ser Lys Pro Asn Arg Glu Arg Gln Lys Leu Met Arg Glu
            500                 505                 510
Gln Asn Ile Leu Lys Gln Ile Phe Lys Leu Leu Gln Ala Pro Phe Thr
        515                 520                 525
Asp Cys Gly Asp Gly Pro Met Leu Arg Leu Glu Glu Leu Gly Asp Gln
    530                 535                 540
Arg His Ala Pro Phe Arg His Ile Cys Arg Leu Cys Tyr Arg Val Leu
545                 550                 555                 560
Arg His Ser Gln Gln Asp Tyr Arg Lys Asn Gln Glu Tyr Ile Ala Lys
                565                 570                 575
Gln Phe Gly Phe Met Gln Lys Gln Ile Gly Tyr Asp Val Leu Ala Glu
            580                 585                 590
Asp Thr Ile Thr Ala Leu Leu His Asn Asn Arg Lys Leu Leu Glu Lys
        595                 600                 605
His Ile Thr Ala Ala Glu Ile Asp Thr Phe Val Ser Leu Val Arg Lys
    610                 615                 620
Asn Arg Glu Pro Arg Phe Leu Asp Tyr Leu Ser Asp Leu Cys Val Ser
625                 630                 635                 640
Met Asn Lys Ser Ile Pro Val Thr Gln Glu Leu Ile Cys Lys Ala Val
                645                 650                 655
Leu Asn Pro Thr Asn Ala Asp Ile Leu Ile Glu Thr Lys Leu Val Leu
            660                 665                 670
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Ser Arg Phe Glu Phe Glu Gly Val Ser Thr Gly Glu Asn Ala Leu Glu
        675                 680                 685
Ala Gly Glu Asp Glu Glu Glu Val Trp Leu Phe Trp Arg Asp Ser Asn
    690                 695                 700
Lys Glu Ile Arg Ser Lys Ser Val Arg Glu Leu Ala Gln Asp Ala Lys
705                 710                 715                 720
Glu Gly Gln Lys Glu Asp Arg Asp Val Leu Ser Tyr Tyr Arg Tyr Gln
                725                 730                 735
Leu Asn Leu Phe Ala Arg Met Cys Leu Asp Arg Gln Tyr Leu Ala Ile
            740                 745                 750
Asn Glu Ile Ser Gly Gln Leu Asp Val Asp Leu Ile Leu Arg Cys Met
        755                 760                 765
Ser Asp Glu Asn Leu Pro Tyr Asp Leu Arg Ala Ser Phe Cys Arg Leu
    770                 775                 780
Met Leu His Met His Val Asp Arg Asp Pro Gln Glu Gln Val Thr Pro
785                 790                 795                 800
Val Lys Tyr Ala Arg Leu Trp Ser Glu Ile Pro Ser Glu Ile Ala Ile
                805                 810                 815
Asp Asp Tyr Asp Ser Ser Gly Ala Ser Lys Asp Glu Ile Lys Glu Arg
            820                 825                 830
Phe Ala Gln Thr Met Glu Phe Val Glu Glu Tyr Leu Arg Asp Val Val
        835                 840                 845
Cys Gln Arg Phe Pro Phe Ser Asp Lys Glu Lys Asn Lys Leu Thr Phe
    850                 855                 860
Glu Val Val Asn Leu Ala Arg Asn Leu Ile Tyr Phe Gly Phe Tyr Asn
865                 870                 875                 880
Phe Ser Asp Leu Leu Arg Leu Thr Lys Ile Leu Leu Ala Ile Leu Asp
                885                 890                 895
Cys Val His Val Thr Thr Ile Phe Pro Ile Ser Lys Met Thr Lys Gly
            900                 905                 910
Glu Glu Asn Lys Gly Ser Asn Val Met Arg Ser Ile His Gly Val Gly
        915                 920                 925
Glu Leu Met Thr Gln Val Val Leu Arg Gly Gly Gly Phe Leu Pro Met
    930                 935                 940
Thr Pro Met Ala Ala Ala Pro Glu Gly Asn Val Lys Gln Ala Glu Pro
945                 950                 955                 960
Glu Lys Glu Asp Ile Met Val Met Asp Thr Lys Leu Lys Ile Ile Glu
                965                 970                 975
Ile Leu Gln Phe Ile Leu Asn Val Arg Leu Asp Tyr Arg Ile Ser Cys
            980                 985                 990
Leu Leu Cys Ile Phe Lys Arg Glu Phe Asp Glu Ser Asn Ser Gln Ser
        995                 1000                1005
Ser Glu Thr Ser Ser Gly Asn Ser Ser Gln Glu Gly Pro Ser Asn Val
    1010                1015                1020
Pro Gly Ala Leu Asp Phe Glu His Ile Glu Glu Gln Ala Glu Gly Ile
1025                1030                1035                1040
Phe Gly Gly Ser Glu Glu Asn Thr Pro Leu Asp Leu Asp Asp His Gly
                1045                1050                1055
Gly Arg Thr Phe Leu Arg Val Leu Leu His Leu Thr Met His Asp Tyr
            1060                1065                1070
Pro Pro Leu Val Ser Gly Ala Leu Gln Leu Leu Phe Arg His Phe Ser
        1075                1080                1085
Gln Arg Gln Glu Val Leu Gln Ala Phe Lys Gln Val Gln Leu Leu Val
    1090                1095                1100
Thr Ser Gln Asp Val Asp Asn Tyr Lys Gln Ile Lys Gln Asp Leu Asp
1105                1110                1115                1120
Gln Leu Arg Ser Ile Val Glu Lys Ser Glu Leu Trp Val Tyr Lys Gly
                1125                1130                1135
Gln Gly Pro Asp Glu Pro Met Asp Gly Ala Ser Gly Glu Asn Glu His
            1140                1145                1150
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Lys Lys Thr Glu Glu Gly Thr Ser Lys Pro Leu Lys His Glu Ser Thr
1155 1160 1165
Ser Ser Tyr Asn Tyr Arg Val Val Lys Glu Ile Leu Ile Arg Leu Ser
1170 1175 1180
Lys Leu Cys Val Gln Glu Ser Ala Ser Val Arg Lys Ser Arg Lys Gln
1185 1190 1195 1200
Gln Gln Arg Leu Leu Arg Asn Met Gly Ala His Ala Val Val Leu Glu
1205 1210 1215
Leu Leu Gln Ile Pro Tyr Glu Lys Ala Glu Asp Thr Lys Met Gln Glu
1220 1225 1230
Ile Met Arg Leu Ala His Glu Phe Leu Gln Asn Phe Cys Ala Gly Asn
1235 1240 1245
Gln Gln Asn Gln Ala Leu Leu His Lys His Ile Asn Leu Phe Leu Asn
1250 1255 1260
Pro Gly Ile Leu Glu Ala Val Thr Met Gln His Ile Phe Met Asn Asn
1265 1270 1275 1280
Phe Gln Leu Cys Ser Glu Ile Asn Glu Arg Val Val Gln His Phe Val
1285 1290 1295
His Cys Ile Glu Thr His Gly Arg Asn Val Gln Tyr Ile Lys Phe Leu
1300 1305 1310
Gln Thr Ile Val Lys Ala Glu Gly Lys Phe Ile Lys Lys Cys Gln Asp
1315 1320 1325
Met Val Met Ala Glu Leu Val Asn Ser Gly Glu Asp Val Leu Val Phe
1330 1335 1340
Tyr Asn Asp Arg Ala Ser Phe Gln Thr Leu Ile Gln Met Met Arg Ser
1345 1350 1355 1360
Glu Arg Asp Arg Met Asp Glu Asn Ser Pro Leu Phe Met Tyr His Ile
1365 1370 1375
His Leu Val Glu Leu Leu Ala Val Cys Thr Glu Gly Lys Asn Val Tyr
1380 1385 1390
Thr Glu Ile Lys Cys Asn Ser Leu Leu Pro Leu Asp Asp Ile Val Arg
1395 1400 1405
Val Val Thr His Glu Asp Cys Ile Pro Glu Val Lys Ile Ala Tyr Ile
1410 1415 1420
Asn Phe Leu Asn His Cys Tyr Val Asp Thr Glu Val Glu Met Lys Glu
1425 1430 1435 1440
Ile Tyr Thr Ser Asn His Met Trp Lys Leu Phe Glu Asn Phe Leu Val
1445 1450 1455
Asp Ile Cys Arg Ala Cys Asn Asn Thr Ser Asp Arg Lys His Ala Asp
1460 1465 1470
Ser Val Leu Glu Lys Tyr Val Thr Glu Ile Val Met Ser Ile Val Thr
1475 1480 1485
Thr Phe Phe Ser Ser Pro Phe Ser Asp Gln Ser Thr Thr Leu Gln Thr
1490 1495 1500
Arg Gln Pro Val Phe Val Gln Leu Leu Gln Gly Val Phe Arg Val Tyr
1505 1510 1515 1520
His Cys Asn Trp Leu Met Pro Ser Gln Lys Ala Ser Val Glu Ser Cys
1525 1530 1535
Ile Arg Val Leu Ser Asp Val Ala Lys Ser Arg Ala Ile Ala Ile Pro
1540 1545 1550
Val Asp Leu Asp Ser Gln Val Asn Asn Leu Phe Leu Lys Ser His Asn
1555 1560 1565
Ile Val Gln Lys Thr Ala Met Asn Trp Arg Leu Ser Ala Arg Asn Ala
1570 1575 1580
Ala Arg Arg Asp Ser Val Leu Ala Ala Ser Arg Asp Tyr Arg Asn Ile
1585 1590 1595 1600
Ile Glu Arg Leu Gln Asp Ile Val Ser Ala Leu Glu Asp Arg Leu Arg
1605 1610 1615
Pro Leu Val Gln Ala Glu Leu Ser Val Leu Val Asp Val Leu His Arg
1620 1625 1630

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Pro Glu Leu Leu Phe Pro Glu Asn Thr Asp Ala Arg Arg Lys Cys Glu
        1635                1640                1645
Ser Gly Gly Phe Ile Cys Lys Leu Ile Lys His Thr Lys Gln Leu Leu
    1650                1655                1660
Glu Glu Asn Glu Glu Lys Leu Cys Ile Lys Val Leu Gln Thr Leu Arg
1665                1670                1675                1680
Glu Met Met Thr Lys Asp Arg Gly Tyr Gly Glu Lys Gln Ile Ser Ile
                1685                1690                1695
Asp Glu Leu Glu Asn Ala Glu Leu Pro Gln Pro Pro Glu Ala Glu Asn
            1700                1705                1710
Ser Thr Glu Glu Leu Glu Pro Ser Pro Pro Leu Arg Gln Leu Glu Asp
        1715                1720                1725
His Lys Arg Gly Glu Ala Leu Arg Gln Ile Leu Val Asn Arg Tyr Tyr
    1730                1735                1740
Gly Asn Ile Arg Pro Ser Gly Arg Arg Glu Ser Leu Thr Ser Phe Gly
1745                1750                1755                1760
Asn Gly Pro Leu Ser Pro Gly Gly Pro Ser Lys Pro Gly Gly Gly Gly
                1765                1770                1775
Gly Gly Pro Gly Ser Gly Ser Thr Ser Arg Gly Glu Met Ser Leu Ala
            1780                1785                1790
Glu Val Gln Cys His Leu Asp Lys Glu Gly Ala Ser Asn Leu Val Ile
        1795                1800                1805
Asp Leu Ile Met Asn Ala Ser Ser Asp Arg Val Phe His Glu Ser Ile
    1810                1815                1820
Leu Leu Ala Ile Ala Leu Leu Glu Gly Gly Asn Thr Thr Ile Gln His
1825                1830                1835                1840
Ser Phe Phe Cys Arg Leu Thr Glu Asp Lys Lys Ser Glu Lys Phe Phe
                1845                1850                1855
Lys Val Phe Tyr Asp Arg Met Lys Val Ala Gln Gln Glu Ile Lys Ala
            1860                1865                1870
Thr Val Thr Val Asn Thr Ser Asp Leu Gly Asn Lys Lys Lys Asp Asp
        1875                1880                1885
Glu Val Asp Arg Asp Ala Pro Ser Arg Lys Lys Ala Lys Glu Pro Thr
    1890                1895                1900
Thr Gln Ile Thr Glu Glu Val Arg Asp Gln Leu Leu Glu Ala Ser Ala
1905                1910                1915                1920
Ala Thr Arg Lys Ala Phe Thr Thr Phe Arg Arg Glu Ala Asp Pro Asp
                1925                1930                1935
Asp His Tyr Gln Ser Gly Glu Gly Thr Gln Ala Thr Thr Asp Lys Ala
            1940                1945                1950
Lys Asp Asp Leu Glu Met Ser Ala Val Ile Thr Ile Met Gln Pro Ile
        1955                1960                1965
Leu Arg Phe Leu Gln Leu Leu Cys Glu Asn His Asn Arg Asp Leu Gln
    1970                1975                1980
Asn Phe Leu Arg Cys Gln Asn Asn Lys Thr Asn Tyr Asn Leu Val Cys
1985                1990                1995                2000
Glu Thr Leu Gln Phe Leu Asp Cys Ile Cys Gly Ser Thr Thr Gly Gly
                2005                2010                2015
Leu Gly Leu Leu Gly Leu Tyr Ile Asn Glu Lys Asn Val Ala Leu Ile
            2020                2025                2030
Asn Gln Thr Leu Glu Ser Leu Thr Glu Tyr Cys Gln Gly Pro Cys His
        2035                2040                2045
Glu Asn Gln Asn Cys Ile Ala Thr His Glu Ser Asn Gly Ile Asp Ile
    2050                2055                2060
Ile Thr Ala Leu Ile Leu Asn Asp Ile Asn Pro Leu Gly Lys Lys Arg
2065                2070                2075                2080
Met Asp Leu Val Leu Glu Leu Lys Asn Asn Ala Ser Lys Leu Leu Leu
                2085                2090                2095
Ala Ile Met Glu Ser Arg His Asp Ser Glu Asn Ala Glu Arg Ile Leu
            2100                2105                2110
```

```
Tyr Asn Met Arg Pro Lys Glu Leu Val Glu Val Ile Lys Lys Ala Tyr
        2115                2120                2125
Met Gln Gly Glu Val Glu Phe Glu Asp Gly Glu Asn Gly Glu Asp Gly
    2130                2135                2140
Ala Ala Ser Pro Arg Asn Val Gly His Asn Ile Tyr Ile Leu Ala His
2145                2150                2155                2160
Gln Leu Ala Arg His Asn Lys Glu Leu Gln Thr Met Leu Lys Pro Gly
                2165                2170                2175
Gly Gln Val Asp Gly Asp Glu Ala Leu Glu Phe Tyr Ala Lys His Thr
            2180                2185                2190
Ala Gln Ile Glu Ile Val Arg Leu Asp Arg Thr Met Glu Gln Ile Val
        2195                2200                2205
Phe Pro Val Pro Ser Ile Cys Glu Phe Leu Thr Lys Glu Ser Lys Leu
    2210                2215                2220
Arg Ile Tyr Tyr Thr Thr Glu Arg Asp Glu Gln Gly Ser Lys Ile Asn
2225                2230                2235                2240
Asp Phe Phe Leu Arg Ser Glu Asp Leu Phe Asn Glu Met Asn Trp Gln
                2245                2250                2255
Lys Lys Leu Arg Ala Gln Pro Val Leu Tyr Trp Cys Ala Arg Asn Met
            2260                2265                2270
Ser Phe Trp Ser Ser Ile Ser Phe Asn Leu Ala Val Leu Met Asn Leu
        2275                2280                2285
Leu Val Ala Phe Phe Tyr Pro Phe Lys Gly Val Arg Gly Gly Thr Leu
    2290                2295                2300
Glu Pro His Trp Ser Gly Leu Leu Trp Thr Ala Met Leu Ile Ser Leu
2305                2310                2315                2320
Ala Ile Val Ile Ala Leu Pro Lys Pro His Gly Ile Arg Ala Leu Ile
                2325                2330                2335
Ala Ser Thr Ile Leu Arg Leu Ile Phe Ser Val Gly Leu Gln Pro Thr
            2340                2345                2350
Leu Phe Leu Leu Gly Ala Phe Asn Val Cys Asn Lys Ile Ile Phe Leu
        2355                2360                2365
Met Ser Phe Val Gly Asn Cys Gly Thr Phe Thr Arg Gly Tyr Arg Ala
    2370                2375                2380
Met Val Leu Asp Val Glu Phe Leu Tyr His Leu Leu Tyr Leu Leu Ile
2385                2390                2395                2400
Cys Ala Met Gly Leu Phe Val His Glu Phe Phe Tyr Ser Leu Leu Leu
                2405                2410                2415
Phe Asp Leu Val Tyr Arg Glu Glu Thr Leu Leu Asn Val Ile Lys Ser
            2420                2425                2430
Val Thr Arg Asn Gly Arg Pro Ile Ile Leu Thr Ala Ala Leu Ala Leu
        2435                2440                2445
Ile Leu Val Tyr Leu Phe Ser Ile Val Gly Tyr Leu Phe Phe Lys Asp
    2450                2455                2460
Asp Phe Ile Leu Glu Val Asp Arg Leu Pro Asn Glu Thr Ala Gly Pro
2465                2470                2475                2480
Glu Thr Gly Glu Ser Leu Ala Asn Asp Phe Leu Tyr Ser Asp Val Cys
                2485                2490                2495
Arg Val Glu Thr Gly Glu Asn Cys Thr Ser Pro Ala Pro Lys Glu Glu
            2500                2505                2510
Leu Leu Pro Val Glu Glu Thr Glu Gln Asp Lys Glu His Thr Cys Glu
        2515                2520                2525
Thr Leu Leu Met Cys Ile Val Thr Val Leu Ser His Gly Leu Arg Ser
    2530                2535                2540
Gly Gly Gly Val Gly Asp Val Leu Arg Lys Pro Ser Lys Glu Glu Pro
2545                2550                2555                2560
Leu Phe Ala Ala Arg Val Ile Tyr Asp Leu Leu Phe Phe Phe Met Val
                2565                2570                2575
Ile Ile Ile Val Leu Asn Leu Ile Phe Gly Val Ile Ile Asp Thr Phe
            2580                2585                2590
```

```
Ala Asp Leu Arg Ser Glu Lys Gln Lys Lys Glu Glu Ile Leu Lys Thr
        2595                2600                2605
Thr Cys Phe Ile Cys Gly Leu Glu Arg Asp Lys Phe Asp Asn Lys Thr
    2610                2615                2620
Val Thr Phe Glu Glu His Ile Lys Glu Glu His Asn Met Trp His Tyr
2625                2630                2635                2640
Leu Cys Phe Ile Val Leu Val Lys Val Lys Asp Ser Thr Glu Tyr Thr
                2645                2650                2655
Gly Pro Glu Ser Tyr Val Ala Glu Met Ile Arg Glu Arg Asn Leu Asp
            2660                2665                2670
Trp Phe Pro Arg Met Arg Ala Met Ser Leu Val Ser Ser Asp Ser Glu
        2675                2680                2685
Gly Glu Gln Asn Glu Leu Arg Asn Leu Gln Glu Lys Leu Glu Ser Thr
    2690                2695                2700
Met Lys Leu Val Thr Asn Leu Ser Gly Gln Leu Ser Glu Leu Lys Asp
2705                2710                2715                2720
Gln Met Thr Glu Gln Arg Lys Gln Lys Gln Arg Ile Gly Leu Leu Gly
                2725                2730                2735
His Pro Pro His Met Asn Val Asn Pro Gln Gln Pro Ala
            2740                2745


<210> 19
<211> 2701
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/note =
      synthetic construct

<400> 19
Met Ser Asp Lys Met Ser Ser Phe Leu Tyr Ile Gly Asp Ile Val Ser
 1               5                  10                  15
Leu Tyr Ala Glu Gly Ser Val Asn Gly Phe Ile Ser Thr Leu Gly Leu
            20                  25                  30
Val Asp Asp Arg Cys Val Val His Pro Glu Ala Gly Asp Leu Thr Asn
        35                  40                  45
Pro Pro Lys Lys Phe Arg Asp Cys Leu Phe Lys Val Cys Pro Met Asn
    50                  55                  60
Arg Tyr Ser Ala Gln Lys Gln Tyr Trp Lys Ala Lys Gln Ala Lys Gln
65                  70                  75                  80
Gly Asn His Thr Glu Ala Ala Leu Leu Lys Lys Leu Gln His Ala Ala
                85                  90                  95
Glu Leu Glu Gln Lys Gln Asn Glu Ser Glu Asn Arg Lys Leu Leu Gly
            100                 105                 110
Glu Ile Val Lys Tyr Ser Lys Val Ile Gln Leu Leu His Ile Lys Ser
        115                 120                 125
Asn Lys Tyr Leu Thr Val Asn Lys Arg Leu Pro Ala Leu Leu Glu Lys
    130                 135                 140
Asn Ala Met Arg Val Ser Leu Asp Ala Ala Gly Asn Glu Gly Ser Trp
145                 150                 155                 160
Phe Tyr Ile His Pro Phe Trp Lys Leu Arg Ser Glu Gly Asp Asn Ile
                165                 170                 175
Val Val Gly Asp Lys Val Val Leu Met Pro Val Asn Ala Gly Gln Pro
            180                 185                 190
Leu His Ala Ser Asn Val Glu Leu Leu Asp Asn Pro Gly Cys Lys Glu
        195                 200                 205
Val Asn Ala Val Asn Cys Asn Thr Ser Trp Lys Ile Thr Leu Phe Met
    210                 215                 220
```

```
Lys Phe Ser Ser Tyr Arg Glu Asp Val Leu Lys Gly Gly Asp Val Val
225                 230                 235                 240
Arg Leu Phe His Ala Glu Gln Glu Lys Phe Leu Thr Cys Asp Asp Tyr
                245                 250                 255
Glu Lys Lys Gln His Ile Phe Leu Arg Thr Thr Leu Arg Gln Ser Ala
            260                 265                 270
Thr Ser Ala Thr Ser Ser Lys Ala Leu Trp Glu Ile Glu Val Val His
        275                 280                 285
His Asp Pro Cys Arg Gly Gly Ala Gly Gln Trp Asn Ser Leu Phe Arg
    290                 295                 300
Phe Lys His Leu Ala Thr Gly Asn Tyr Leu Ala Ala Glu Leu Asn Pro
305                 310                 315                 320
Asp Tyr Arg Asp Ala Gln Asn Glu Gly Lys Thr Val Arg Asp Gly Glu
                325                 330                 335
Leu Pro Thr Ser Lys Lys Lys His Gln Ala Gly Glu Lys Ile Met Tyr
            340                 345                 350
Thr Leu Val Ser Val Pro His Gly Asn Asp Ile Ala Ser Leu Phe Glu
        355                 360                 365
Leu Asp Ala Thr Thr Leu Gln Arg Ala Asp Cys Leu Val Pro Arg Asn
    370                 375                 380
Ser Tyr Val Arg Leu Arg His Leu Cys Thr Asn Thr Trp Val Thr Ser
385                 390                 395                 400
Thr Ser Ile Pro Ile Asp Thr Glu Glu Glu Arg Pro Val Met Leu Lys
                405                 410                 415
Ile Gly Thr Cys Gln Thr Lys Glu Asp Lys Glu Ala Phe Ala Ile Val
            420                 425                 430
Cys Val Pro Leu Ser Glu Val Arg Asp Leu Asp Phe Ala Asn Asp Ala
        435                 440                 445
Asn Lys Val Leu Ala Thr Thr Val Lys Lys Leu Glu Asn Gly Ser Ile
    450                 455                 460
Thr Gln Asn Glu Arg Arg Phe Val Thr Lys Leu Leu Glu Asp Leu Ile
465                 470                 475                 480
Phe Phe Val Ala Asp Val Thr Asn Asn Gly Gln Asp Val Leu Asp Val
                485                 490                 495
Val Ile Thr Lys Pro Asn Arg Glu Arg Gln Lys Leu Met Arg Glu Gln
            500                 505                 510
Asn Ile Leu Ala Gln Val Phe Gly Ile Leu Lys Ala Pro Phe Lys Glu
        515                 520                 525
Lys Ala Gly Glu Gly Ser Met Leu Arg Leu Glu Asp Leu Gly Asp Gln
    530                 535                 540
Arg Tyr Ala Pro Tyr Lys Tyr Val Leu Arg Leu Cys Tyr Arg Val Leu
545                 550                 555                 560
Arg His Ser Gln Gln Asp Tyr Arg Lys Asn Gln Glu Tyr Ile Ala Lys
                565                 570                 575
Asn Phe Cys Val Met Gln Ser Gln Ile Gly Tyr Asp Ile Leu Ala Glu
            580                 585                 590
Asp Thr Ile Thr Ala Leu Leu His Asn Asn Arg Lys Leu Leu Glu Lys
        595                 600                 605
His Ile Thr Ala Lys Glu Ile Glu Thr Phe Val Ser Leu Leu Arg Arg
    610                 615                 620
Asn Arg Glu Pro Arg Phe Leu Asp Tyr Leu Ser Asp Leu Cys Val Ser
625                 630                 635                 640
Asn Ser Thr Ala Ile Pro Val Thr Gln Glu Leu Ile Cys Lys Phe Met
                645                 650                 655
Leu Ser Pro Gly Asn Ala Asp Ile Leu Ile Gln Thr Lys Leu Val Ser
            660                 665                 670
Met Gln Val Glu Asn Pro Met Glu Ser Ser Ile Leu Pro Asp Asp Ile
        675                 680                 685
Asp Asp Glu Glu Val Trp Leu Tyr Trp Ile Asp Ser Asn Lys Glu Pro
    690                 695                 700
```

```
His Gly Lys Ala Ile Arg His Leu Ala Gln Glu Ala Arg Glu Gly Thr
705                 710                 715                 720
Lys Ala Asp Leu Glu Val Leu Thr Tyr Tyr Arg Tyr Gln Leu Asn Leu
                725                 730                 735
Phe Ala Arg Met Cys Leu Asp Arg Gln Tyr Leu Ala Ile Asn Gln Ile
            740                 745                 750
Ser Thr Gln Leu Ser Val Asp Leu Ile Leu Arg Cys Val Ser Asp Glu
        755                 760                 765
Ser Leu Pro Phe Asp Leu Arg Ala Ser Phe Cys Arg Leu Met Leu His
    770                 775                 780
Met His Val Asp Arg Asp Pro Gln Glu Ser Val Val Pro Val Arg Tyr
785                 790                 795                 800
Ala Arg Leu Trp Thr Glu Ile Pro Thr Lys Ile Thr Ile His Glu Tyr
                805                 810                 815
Asp Ser Ile Thr Asp Ser Ser Arg Asn Asp Met Lys Arg Lys Phe Ala
            820                 825                 830
Leu Thr Met Glu Phe Val Glu Glu Tyr Leu Lys Glu Val Val Asn Gln
        835                 840                 845
Pro Phe Pro Phe Gly Asp Lys Glu Lys Asn Lys Leu Thr Phe Glu Val
    850                 855                 860
Val His Leu Ala Arg Asn Leu Ile Tyr Phe Gly Phe Tyr Ser Phe Ser
865                 870                 875                 880
Glu Leu Leu Arg Leu Thr Arg Thr Leu Leu Ala Ile Leu Asp Ile Val
                885                 890                 895
Gln Ala Pro Met Ser Ser Tyr Phe Glu Arg Leu Ser Lys Phe Gln Asp
            900                 905                 910
Gly Ser Asn Asn Val Met Arg Thr Ile His Gly Val Gly Glu Met Met
        915                 920                 925
Thr Gln Met Val Leu Ser Arg Gly Ser Ile Phe Pro Val Ser Trp Pro
    930                 935                 940
Asp Ala Gln Pro Ser Val His Pro Ser Lys Gln Ala Ser Pro Gly Glu
945                 950                 955                 960
Gln Glu Asp Val Thr Val Met Asp Thr Lys Leu Lys Val Ile Glu Ile
                965                 970                 975
Leu Gln Phe Ile Leu Ser Val Arg Leu Asp Tyr Arg Ile Ser Tyr Met
            980                 985                 990
Leu Ser Ile Tyr Lys Lys Glu Phe Gly Glu Asn Asp Gly Asn Gly Asp
        995                 1000                1005
Pro Ser Ala Ser Gly Thr Pro Glu Thr Leu Leu Pro Ser Ala Leu Val
    1010                1015                1020
Pro Asp Ile Asp Glu Ile Ala Ala Gln Ala Glu Thr Met Phe Ala Gly
1025                1030                1035                1040
Arg Lys Glu Lys Thr Pro Val Gln Leu Asp Asp Glu Gly Gly Arg Thr
                1045                1050                1055
Phe Leu Arg Val Leu Ile His Leu Ile Met His Asp Tyr Ala Pro Leu
            1060                1065                1070
Leu Ser Gly Ala Leu Gln Leu Leu Phe Lys His Phe Ser Gln Arg Ala
        1075                1080                1085
Glu Val Leu Gln Ala Phe Lys Gln Val Gln Leu Leu Val Ser Asn Gln
    1090                1095                1100
Asp Val Asp Asn Tyr Lys Gln Ile Lys Ala Asp Leu Asp Gln Leu Arg
1105                1110                1115                1120
Leu Thr Val Glu Lys Ser Glu Leu Trp Val Glu Lys Ser Gly Ser Tyr
                1125                1130                1135
Glu Asn Gly Asp Met Gly Glu Gly Gln Ala Lys Gly Gly Glu Glu Ala
            1140                1145                1150
Asn Glu Glu Ser Asn Leu Leu Ser Pro Val Gln Asp Gly Ala Lys Thr
        1155                1160                1165
Pro Gln Ile Asp Ser Asn Lys Gly Asn Asn Tyr Arg Ile Val Lys Glu
    1170                1175                1180
```

```
Ile Leu Ile Arg Leu Ser Lys Leu Cys Val Gln Asn Lys Lys Cys Arg
1185                1190                1195                1200
Asn Gln His Gln Arg Leu Leu Lys Asn Met Gly Ala His Ser Val Val
                1205                1210                1215
Leu Asp Leu Leu Gln Ile Pro Tyr Glu Lys Thr Asp Glu Lys Met Asn
            1220                1225                1230
Glu Val Met Asp Leu Ala His Thr Phe Leu Gln Asn Phe Cys Arg Gly
        1235                1240                1245
Asn Pro Gln Asn Gln Val Leu Leu His Lys His Leu Asn Leu Phe Leu
    1250                1255                1260
Thr Pro Gly Leu Leu Glu Ala Glu Thr Met Arg His Ile Phe Met Asn
1265                1270                1275                1280
Asn Tyr His Leu Cys Asn Glu Ile Ser Glu Arg Val Val Gln His Phe
                1285                1290                1295
Val His Cys Ile Glu Thr His Gly Arg His Val Glu Tyr Leu Arg Phe
            1300                1305                1310
Leu Gln Thr Ile Val Lys Ala Asp Gly Lys Tyr Val Lys Lys Cys Gln
        1315                1320                1325
Asp Met Val Met Thr Glu Leu Ile Asn Gly Gly Glu Asp Val Leu Ile
    1330                1335                1340
Phe Tyr Asn Asp Arg Ala Ser Phe Pro Ile Leu Leu Asn Met Met Cys
1345                1350                1355                1360
Ser Glu Arg Ala Arg Gly Asp Glu Ser Gly Pro Leu Ala Tyr His Ile
                1365                1370                1375
Thr Leu Val Glu Leu Leu Ala Ala Cys Thr Glu Gly Lys Asn Val Tyr
            1380                1385                1390
Thr Glu Ile Lys Cys Asn Ser Leu Leu Pro Leu Asp Asp Ile Val Arg
        1395                1400                1405
Val Val Thr His Asp Asp Cys Ile Pro Glu Val Lys Ile Ala Tyr Val
    1410                1415                1420
Asn Phe Val Asn His Cys Tyr Val Asp Thr Glu Val Glu Met Lys Glu
1425                1430                1435                1440
Ile Tyr Thr Ser Asn His Ile Trp Lys Leu Phe Glu Asn Phe Leu Val
                1445                1450                1455
Asp Met Ala Arg Val Cys Asn Thr Thr Thr Asp Arg Lys His Ala Asp
            1460                1465                1470
Thr Phe Leu Glu Arg Cys Val Thr Glu Ser Val Met Asn Ile Val Ser
        1475                1480                1485
Gly Phe Phe Asn Ser Pro Phe Ser Asp Asn Ser Thr Ser Leu Gln Thr
    1490                1495                1500
His Gln Pro Val Phe Ile Gln Leu Leu Gln Ser Ala Phe Arg Ile Tyr
1505                1510                1515                1520
Asn Cys Thr Trp Pro Asn Pro Ala Gln Lys Ala Ser Val Glu Ser Cys
                1525                1530                1535
Ile Arg Ala Leu Ala Glu Val Ala Lys Asn Arg Gly Ile Ala Ile Pro
            1540                1545                1550
Val Asp Leu Asp Ser Gln Val Asn Thr Leu Phe Met Lys Asn His Ser
        1555                1560                1565
Ser Thr Val Gln Arg Ala Ala Met Gly Trp Arg Leu Ser Ala Arg Ser
    1570                1575                1580
Gly Pro Arg Phe Lys Glu Ala Leu Gly Gly Pro Ala Trp Asp Tyr Arg
1585                1590                1595                1600
Asn Ile Ile Glu Lys Leu Gln Asp Val Val Ala Ser Leu Glu Gln Gln
                1605                1610                1615
Phe Ser Pro Met Met Gln Ala Glu Phe Ser Val Leu Val Asp Val Leu
            1620                1625                1630
Tyr Ser Pro Glu Leu Leu Phe Pro Glu Gly Ser Asp Ala Arg Ile Arg
        1635                1640                1645
Cys Gly Ala Phe Met Ser Lys Leu Ile Asn His Thr Lys Lys Leu Met
    1650                1655                1660
```

```
Glu Lys Glu Glu Lys Leu Cys Ile Lys Ile Leu Gln Thr Leu Arg Glu
1665                1670                1675                1680
Met Leu Glu Lys Lys Asp Ser Phe Met Glu Glu Ser Ser Thr Leu Arg
                1685                1690                1695
Lys Ile Leu Leu Asn Arg Tyr Phe Lys Gly Asp His Ser Val Gly Val
            1700                1705                1710
Asn Gly Pro Leu Ser Gly Ala Tyr Ala Lys Thr Ala Gln Val Gly Gly
        1715                1720                1725
Gly Phe Thr Gly Gln Asp Ala Asp Lys Thr Gly Ile Ser Met Ser Asp
    1730                1735                1740
Ile Gln Cys Leu Leu Asp Lys Glu Gly Ala Ser Glu Leu Val Ile Asp
1745                1750                1755                1760
Val Ile Val Asn Thr Lys Asn Asp Arg Ile Phe Ser Glu Gly Ile Leu
                1765                1770                1775
Leu Gly Ile Ala Leu Leu Glu Gly Gly Asn Thr Gln Thr Gln Asn Ser
            1780                1785                1790
Phe Tyr Gln Gln Leu His Glu Gln Lys Lys Ser Glu Lys Phe Phe Lys
        1795                1800                1805
Val Leu Tyr Asp Arg Met Lys Ala Ala Gln Lys Glu Ile Arg Ser Thr
    1810                1815                1820
Val Thr Val Asn Thr Ile Asp Leu Gly Ser Lys Lys Arg Glu Glu Asp
1825                1830                1835                1840
Ser Asp Leu Met Ala Leu Gly Pro Arg Met Arg Val Arg Asp Ser Ser
                1845                1850                1855
Leu His Leu Lys Glu Gly Met Lys Gly Gln Leu Thr Glu Ala Ser Ser
            1860                1865                1870
Ala Thr Ser Lys Ala Tyr Cys Val Tyr Arg Arg Glu Met Asp Pro Asp
        1875                1880                1885
Ile Asp Thr Met Cys Pro Gly Gln Glu Ala Gly Ser Ala Glu Glu Lys
    1890                1895                1900
Ser Ala Glu Glu Val Thr Met Ser Pro Ala Ile Thr Ile Met Arg Pro
1905                1910                1915                1920
Ile Leu Arg Phe Leu Gln Leu Leu Cys Glu Asn His Asn Arg Glu Leu
                1925                1930                1935
Gln Asn Phe Leu Arg Asn Gln Asn Asn Lys Thr Asn Tyr Asn Leu Val
            1940                1945                1950
Cys Glu Thr Leu Gln Phe Leu Asp Cys Ile Cys Gly Ser Thr Thr Gly
        1955                1960                1965
Gly Leu Gly Leu Leu Gly Leu Tyr Ile Asn Glu Lys Asn Val Ala Leu
    1970                1975                1980
Val Asn Gln Thr Leu Glu Ser Leu Thr Glu Tyr Cys Gln Gly Pro Cys
1985                1990                1995                2000
His Glu Asn Gln Thr Cys Ile Ala Thr His Glu Ser Asn Gly Ile Asp
                2005                2010                2015
Ile Ile Ile Ala Leu Ile Leu Ser Asp Ile Asn Pro Leu Gly Lys Tyr
            2020                2025                2030
Arg Met Asp Leu Val Leu Gln Leu Lys Asn Asn Ala Ser Lys Leu Leu
        2035                2040                2045
Leu Ala Ile Met Glu Ser Arg His Asp Ser Glu Asn Ala Glu Arg Ile
    2050                2055                2060
Leu Phe Asn Met Arg Pro Lys Glu Leu Val Asp Val Met Lys Asn Ala
2065                2070                2075                2080
Tyr Asn Gln Gly Leu Glu Cys Asn His Gly Asp Glu Glu Gly Gly Asp
                2085                2090                2095
Asp Gly Val Ser Pro Lys Asp Val Gly His Asn Ile Tyr Ile Leu Ala
            2100                2105                2110
His Gln Leu Ala Arg His Asn Lys Leu Leu Gln Gln Met Leu Lys Pro
        2115                2120                2125
Gly Ser Asp Pro Glu Glu Gly Asp Glu Ala Leu Lys Tyr Tyr Ala Asn
    2130                2135                2140
```

```
His Thr Ala Gln Ile Glu Ile Val Arg His Asp Arg Thr Met Glu Gln
2145                2150                2155                2160
Ile Val Phe Pro Val Pro Asn Ile Cys Glu Phe Leu Thr Arg Glu Ser
                2165                2170                2175
Lys Tyr Arg Val Phe Asn Thr Thr Glu Arg Asp Glu Gln Gly Ser Lys
            2180                2185                2190
Val Asn Asp Phe Phe Gln Gln Thr Glu Asp Leu Tyr Asn Glu Met Lys
        2195                2200                2205
Trp Gln Lys Lys Ile Arg Asn Asn Pro Ala Leu Phe Trp Phe Ser Arg
    2210                2215                2220
His Ile Ser Leu Trp Gly Ser Ile Ser Phe Asn Leu Ala Val Phe Ile
2225                2230                2235                2240
Asn Leu Ala Val Ala Leu Phe Tyr Pro Phe Gly Asp Asp Gly Asp Glu
                2245                2250                2255
Gly Thr Leu Ser Pro Leu Phe Ser Ala Leu Leu Trp Val Ala Val Ala
            2260                2265                2270
Ile Cys Thr Ser Met Leu Phe Phe Phe Ser Lys Pro Val Gly Ile Arg
        2275                2280                2285
Pro Phe Leu Val Ser Ile Met Leu Arg Ser Ile Tyr Thr Ile Gly Leu
    2290                2295                2300
Gly Pro Thr Leu Ile Leu Leu Gly Ala Ala Asn Leu Cys Asn Lys Ile
2305                2310                2315                2320
Val Phe Leu Val Ser Phe Val Gly Asn Arg Gly Thr Phe Thr Arg Gly
                2325                2330                2335
Tyr Arg Ala Val Ile Leu Asp Met Ala Phe Leu Tyr His Val Ala Tyr
            2340                2345                2350
Val Leu Val Cys Met Leu Gly Leu Phe Val His Glu Phe Phe Tyr Ser
        2355                2360                2365
Phe Leu Leu Phe Asp Leu Val Tyr Arg Glu Glu Thr Leu Leu Asn Val
    2370                2375                2380
Ile Lys Ser Val Thr Arg Asn Gly Arg Ser Ile Ile Leu Thr Ala Val
2385                2390                2395                2400
Leu Ala Leu Ile Leu Val Tyr Leu Phe Ser Ile Ile Gly Phe Leu Phe
                2405                2410                2415
Leu Lys Asp Asp Phe Thr Met Glu Val Asp Arg Leu Lys Asn Arg Thr
            2420                2425                2430
Pro Val Thr Gly Asn Asp Gly Val Pro Thr Met Thr Leu Thr Ser Met
        2435                2440                2445
Leu Gly Thr Cys Pro Lys Glu Asn Cys Ser Pro Thr Ile Pro Ser Ser
    2450                2455                2460
Asn Ala Ala Gly Glu Gly Gly Glu Asp Gly Ile Glu Arg Thr Cys Asp
2465                2470                2475                2480
Thr Leu Leu Met Cys Ile Val Thr Val Leu Asn Gln Gly Leu Arg Asn
                2485                2490                2495
Gly Gly Gly Val Gly Asp Val Leu Arg Arg Pro Ser Lys Asp Glu Pro
            2500                2505                2510
Leu Phe Ala Ala Arg Val Val Tyr Asp Leu Leu Phe Phe Phe Ile Val
        2515                2520                2525
Ile Ile Ile Val Leu Asn Leu Ile Phe Gly Val Ile Ile Asp Thr Phe
    2530                2535                2540
Ala Asp Leu Arg Ser Glu Lys Gln Lys Lys Glu Lys Ile Leu Lys Thr
2545                2550                2555                2560
Thr Cys Phe Ile Cys Gly Leu Glu Arg Asp Lys Phe Asp Asn Lys Thr
                2565                2570                2575
Val Ser Phe Glu Glu His Ile Lys Ser Glu His Asn Met Trp His Tyr
            2580                2585                2590
Leu Tyr Phe Ile Val Leu Val Lys Val Lys Asp Pro Thr Glu Tyr Thr
        2595                2600                2605
Gly Pro Glu Ser Tyr Val Ala Gln Met Ile Thr Glu Lys Asn Leu Asp
    2610                2615                2620
```

```
Trp Phe Pro Arg Met Arg Ala Met Ser Leu Val Ser Asn Glu Gly Asp
2625                2630                2635                2640
Ser Glu Gln Asn Glu Ile Arg Asn Leu Gln Glu Lys Leu Glu Ser Thr
                    2645                2650                2655
Met Ser Leu Val Lys Gln Leu Ser Gly Gln Leu Ala Glu Leu Lys Glu
            2660                2665                2670
Gln Met Thr Glu Gln Arg Lys Asn Lys Gln Arg Leu Gly Phe Leu Gly
        2675                2680                2685
Ser Asn Thr Pro His Glu Asn His His Met Pro Pro His
    2690                2695                2700


<210> 20
<211> 2670
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/note =
      synthetic construct

<400> 20
Met Asn Glu Met Ser Ser Phe Leu His Ile Gly Asp Ile Val Ser Leu
 1               5                  10                  15
Tyr Ala Glu Gly Ser Val Asn Gly Phe Ile Ser Thr Leu Gly Leu Val
            20                  25                  30
Asp Asp Arg Cys Val Val Glu Pro Ala Ala Gly Asp Leu Asp Asn Pro
        35                  40                  45
Pro Lys Lys Phe Arg Asp Cys Leu Phe Lys Val Cys Pro Met Asn Arg
    50                  55                  60
Tyr Ser Ala Gln Lys Gln Tyr Trp Lys Ala Lys Gln Thr Lys Gln Asp
65                  70                  75                  80
Lys Glu Lys Ile Ala Asp Val Val Leu Leu Gln Lys Leu Gln His Ala
                85                  90                  95
Ala Gln Met Glu Gln Lys Gln Asn Asp Thr Glu Asn Lys Lys Val His
            100                 105                 110
Gly Asp Val Val Lys Tyr Gly Ser Val Ile Gln Leu Leu His Met Lys
        115                 120                 125
Ser Asn Lys Tyr Leu Thr Val Asn Lys Arg Leu Pro Ala Leu Leu Glu
    130                 135                 140
Lys Asn Ala Met Arg Val Thr Leu Asp Ala Thr Gly Asn Glu Gly Ser
145                 150                 155                 160
Trp Leu Phe Ile Gln Pro Phe Trp Lys Leu Arg Ser Asn Gly Asp Asn
                165                 170                 175
Val Val Val Gly Asp Lys Val Ile Leu Asn Pro Val Asn Ala Gly Gln
            180                 185                 190
Pro Leu His Ala Ser Asn Tyr Glu Leu Ser Asp Asn Val Gly Cys Lys
        195                 200                 205
Glu Val Asn Ser Val Asn Cys Asn Thr Ser Trp Lys Ile Asn Leu Phe
    210                 215                 220
Met Gln Phe Arg Asp His Leu Glu Glu Val Leu Lys Gly Gly Asp Val
225                 230                 235                 240
Val Arg Leu Phe His Ala Glu Gln Glu Lys Phe Leu Thr Cys Asp Glu
                245                 250                 255
Tyr Arg Gly Lys Leu Gln Val Phe Leu Arg Thr Thr Leu Arg Gln Ser
            260                 265                 270
Ala Thr Ser Ala Thr Ser Ser Asn Ala Leu Trp Glu Val Glu Val Val
        275                 280                 285
His His Asp Pro Cys Arg Gly Gly Ala Gly His Trp Asn Gly Leu Tyr
    290                 295                 300
```

```
Arg Phe Lys His Leu Ala Thr Gly Asn Tyr Leu Ala Ala Glu Glu Asn
305                 310                 315                 320
Pro Ser Tyr Lys Gly Asp Val Ser Asp Pro Lys Ala Ala Gly Pro Gly
                325                 330                 335
Ala Gln Ser Arg Thr Gly Arg Arg Asn Ala Gly Glu Lys Ile Lys Tyr
            340                 345                 350
Arg Leu Val Ala Val Pro His Gly Asn Asp Ile Ala Ser Leu Phe Glu
        355                 360                 365
Leu Asp Pro Thr Thr Leu Gln Lys Thr Asp Ser Phe Val Pro Arg Asn
    370                 375                 380
Ser Tyr Val Arg Leu Arg His Leu Cys Thr Asn Thr Trp Ile Gln Ser
385                 390                 395                 400
Thr Asn Ala Pro Ile Asp Val Glu Glu Glu Arg Pro Ile Arg Leu Met
                405                 410                 415
Leu Gly Thr Cys Pro Thr Lys Glu Asp Lys Glu Ala Phe Ala Ile Val
            420                 425                 430
Ser Val Pro Val Ser Glu Ile Arg Asp Leu Asp Phe Ala Asn Asp Ala
        435                 440                 445
Ser Ser Met Leu Ala Ser Ala Val Glu Lys Leu Asn Glu Gly Phe Ile
    450                 455                 460
Ser Gln Asn Asp Arg Arg Phe Val Ile Gln Leu Leu Glu Asp Leu Val
465                 470                 475                 480
Phe Phe Val Ser Asp Val Pro Asn Asn Gly Gln Asn Val Leu Asp Ile
                485                 490                 495
Met Val Thr Lys Pro Asn Arg Glu Arg Gln Lys Leu Met Arg Asp Glu
            500                 505                 510
Asn Ile Leu Lys Gln Ile Phe Gly Ile Leu Lys Ala Pro Phe Arg Asp
        515                 520                 525
Lys Gly Gly Glu Gly Pro Leu Val Arg Leu Glu Glu Leu Ser Asp Gln
    530                 535                 540
Lys Asn Ala Pro Tyr Gln Tyr Met Phe Arg Leu Cys Tyr Arg Val Leu
545                 550                 555                 560
Arg His Ser Gln Glu Asp Tyr Arg Lys Asn Gln Glu His Ile Ala Lys
                565                 570                 575
Gln Phe Gly Met Met Gln Ser Gln Ile Gly Tyr Asp Ile Leu Ala Glu
            580                 585                 590
Asp Thr Ile Thr Ala Leu Leu His Asn Asn Arg Lys Leu Leu Glu Lys
        595                 600                 605
His Ile Thr Lys Thr Glu Val Glu Thr Phe Val Ser Leu Val Arg Lys
    610                 615                 620
Asn Arg Glu Pro Arg Phe Leu Asp Tyr Leu Ser Asp Leu Cys Val Ser
625                 630                 635                 640
Asn Arg Ile Ala Ile Pro Val Thr Gln Glu Leu Ile Cys Lys Cys Val
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Leu Asp Pro Lys Asn Ser Asp Ile Leu Ile Gln Thr Glu Leu Arg Pro
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Val Lys Glu Met Ala Gln Ser His Glu Tyr Leu Ser Ile Glu Tyr Ser
        675                 680                 685
Glu Glu Glu Val Trp Leu Thr Trp Thr Asp Arg Asn Asn Glu His His
    690                 695                 700
Glu Lys Ser Val Arg Gln Leu Ala Gln Glu Ala Arg Ala Gly Asn Ala
705                 710                 715                 720
His Asp Glu Asn Val Leu Ser Tyr Tyr Arg Tyr Gln Leu Lys Leu Phe
                725                 730                 735
Ala Arg Met Cys Leu Asp Arg Gln Tyr Leu Ala Ile Asp Glu Ile Ser
            740                 745                 750
Lys Gln Leu Gly Val Glu Leu Leu Phe Leu Cys Met Ala Asp Glu Met
        755                 760                 765
Leu Pro Phe Asp Leu Arg Ala Ser Phe Cys His Leu Met Leu His Val
    770                 775                 780
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Arg Leu Trp Thr Glu Ile Pro Thr Ala Ile Thr Ile Lys Asp Tyr Asp
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Ser Asn Leu Asn Ala Ser Arg Asp Asp Lys Lys Asn Lys Phe Ala Ser
            820                 825                 830
Thr Met Glu Phe Val Glu Asp Tyr Leu Asn Asn Val Val Gly Glu Ala
        835                 840                 845
Val Pro Phe Ala Asn Asp Glu Lys Asn Ile Leu Thr Phe Glu Val Val
    850                 855                 860
Ser Leu Ala His Asn Leu Ile Tyr Phe Gly Phe Tyr Ser Phe Ser Glu
865                 870                 875                 880
Leu Leu Arg Leu Thr Arg Thr Leu Leu Gly Ile Ile Asp Cys Ile Gln
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Ala Pro Ala Ala Val Leu Gln Ala Tyr Glu Glu Pro Gly Gly Lys Asn
            900                 905                 910
Val Arg Arg Ser Ile Gln Gly Val Gly His Met Met Ser Thr Met Val
        915                 920                 925
Leu Ser Arg Lys Gln Ser Val Phe Gly Ala Ser Ser Leu Pro Thr Gly
    930                 935                 940
Val Gly Val Pro Glu Gln Leu Asp Arg Ser Lys Phe Glu Asp Asn Glu
945                 950                 955                 960
His Thr Val Val Met Glu Thr Lys Leu Lys Ile Leu Glu Ile Leu Gln
                965                 970                 975
Phe Ile Leu Asn Val Arg Leu Asp Tyr Arg Ile Ser Tyr Leu Leu Ser
            980                 985                 990
Val Phe Lys Lys Glu Phe Val Glu Val Phe Pro Met Gln Asp Ser Gly
        995                 1000                1005
Ala Asp Gly Thr Ala Pro Ala Phe Asp Ser Ser Thr Ala Asn Met Asn
    1010                1015                1020
Leu Asp Arg Ile Gly Glu Gln Ala Glu Ala Met Phe Gly Val Gly Lys
1025                1030                1035                1040
Thr Ser Ser Met Leu Glu Val Asp Asp Glu Gly Gly Arg Met Phe Leu
                1045                1050                1055
Arg Val Leu Leu His Leu Thr Met His Asp Tyr Pro Pro Leu Val Ser
            1060                1065                1070
Gly Ala Leu Gln Leu Leu Phe Lys His Phe Ser Gln Arg Gln Glu Ala
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Met His Thr Phe Lys Gln Val Gln Leu Leu Ile Ser Ala Gln Asp Val
    1090                1095                1100
Glu Asn Tyr Lys Val Ile Lys Ser Glu Leu Asp Arg Leu Arg Thr Met
1105                1110                1115                1120
Val Glu Lys Ser Glu Leu Trp Val Asp Lys Lys Gly Ser Val Lys Gly
                1125                1130                1135
Glu Glu Gly Glu Ala Gly Ala Ser Lys Asp Lys Lys Glu Arg Pro Ser
            1140                1145                1150
Asp Glu Glu Gly Phe Leu Gln Pro His Gly Glu Lys Ser Ser Glu Asn
        1155                1160                1165
Tyr Gln Ile Val Lys Gly Ile Leu Glu Arg Leu Asn Lys Met Cys Gly
    1170                1175                1180
Val Gly Glu Gln Met Arg Lys Lys Gln Gln Arg Leu Leu Lys Asn Met
1185                1190                1195                1200
Asp Ala His Lys Val Met Leu Asp Leu Leu Gln Ile Pro Tyr Asp Lys
                1205                1210                1215
Asn Asp Asn Lys Met Met Glu Ile Leu Arg Tyr Thr His Gln Phe Leu
            1220                1225                1230
Gln Lys Phe Cys Ala Gly Asn Pro Gly Asn Gln Ala Leu Leu His Lys
        1235                1240                1245
His Leu Gln Leu Phe Leu Thr Pro Gly Leu Leu Glu Ala Glu Thr Met
    1250                1255                1260
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Gln His Ile Phe Leu Asn Asn Tyr Gln Leu Cys Ser Glu Ile Ser Glu
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Pro Val Leu Gln His Phe Val His Cys Trp Pro Thr His Gly Arg His
                1285                1290                1295
Val Gln Tyr Leu Asp Phe Leu His Thr Val Ile Lys Ala Glu Gly Lys
            1300                1305                1310
Tyr Val Lys Lys Cys Gln Asp Met Ile Met Thr Glu Leu Thr Asn Ala
        1315                1320                1325
Gly Asp Asp Val Val Val Phe Tyr Asn Asp Lys Ala Ser Leu Ala His
    1330                1335                1340
Leu Leu Asp Met Met Lys Ala Ala Arg Asp Gly Val Glu Asp His Ser
1345                1350                1355                1360
Pro Leu Met Tyr His Ile Ser Leu Val Asp Leu Leu Ala Ala Cys Ala
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Glu Gly Lys Asn Val Tyr Thr Glu Ile Lys Cys Thr Ser Leu Leu Pro
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Leu Glu Asp Val Val Ser Val Val Thr His Glu Asp Cys Ile Thr Glu
        1395                1400                1405
Val Lys Met Ala Tyr Val Asn Phe Val Asn His Cys Tyr Val Asp Thr
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Glu Val Glu Met Lys Glu Ile Tyr Thr Ser Asn His Ile Trp Thr Leu
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Phe Glu Asn Phe Thr Leu Asp Met Ala Leu Val Cys Asn Lys Arg Glu
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Lys Arg Leu Ser Asp Pro Thr Leu Glu Lys Tyr Val Leu Thr Val Val
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Leu Asp Thr Ile Ser Ala Phe Phe Ser Ser Pro Phe Ser Glu Asn Ser
        1475                1480                1485
Thr Ser Leu Gln Thr His Gln Thr Ile Val Val Gln Leu Leu Gln Ser
    1490                1495                1500
Thr Thr Arg Leu Leu Glu Cys Pro Trp Leu Gln Gln Gln His Lys Gly
1505                1510                1515                1520
Ser Val Glu Ala Cys Val Arg Thr Leu Ala Met Val Ala Lys Ser Arg
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Ala Ile Leu Leu Pro Met Asp Leu Asp Ala His Met Ser Ala Leu Leu
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Ser Ser Gly Gly Ser Cys Ser Ala Ala Ala Gln Arg Ser Ala Ala Asn
        1555                1560                1565
Tyr Lys Thr Ala Thr Arg Thr Phe Pro Arg Val Ile Pro Thr Ala Asn
    1570                1575                1580
Gln Trp Asp Tyr Lys Asn Ile Ile Glu Lys Leu Gln Asp Ile Ile Thr
1585                1590                1595                1600
Ala Leu Glu Glu Arg Leu Lys Pro Leu Val Gln Ala Glu Leu Ser Val
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Leu Val Asp Met Leu His Trp Pro Glu Leu Leu Phe Leu Glu Gly Ser
            1620                1625                1630
Glu Ala Tyr Gln Arg Cys Glu Ser Gly Gly Phe Leu Ser Lys Leu Ile
        1635                1640                1645
Arg His Thr Lys Gly Leu Met Glu Ser Glu Glu Lys Leu Cys Val Lys
    1650                1655                1660
Val Leu Arg Thr Leu Gln Gln Met Leu Gln Lys Lys Ser Lys Tyr Gly
1665                1670                1675                1680
Asp Arg Gly Asn Gln Leu Arg Lys Met Leu Leu Gln Asn Tyr Leu Gln
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Asn Arg Lys Ser Gly Pro Arg Gly Glu Leu Thr Asp Pro Thr Gly Ser
            1700                1705                1710
Gly Val Asp Gln Asp Trp Ser Ala Ile Ala Ala Thr Gln Cys Arg Leu
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Asp Lys Glu Gly Ala Thr Lys Leu Val Cys Asp Leu Ile Thr Ser Thr
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Thr Ser Asp Lys Lys Ser Glu Arg Phe Phe Lys Val Leu His Asp Arg
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Met Lys Arg Ala Gln Gln Glu Thr Lys Ser Thr Val Ala Val Asn Met
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Ser Asp Leu Gly Ser Gln Pro Arg Glu Asp Arg Glu Pro Ala Asp Pro
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Thr Thr Lys Gly Arg Val Ser Ser Phe Ser Met Pro Ser Ser Ser Arg
1825                1830                1835                1840
Tyr Ser Leu Gly Pro Gly Leu His Arg Gly His Asp Val Ser Glu Arg
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Ala Gln Asn Asn Glu Met Gly Thr Ser Val Leu Ile Met Arg Pro Ile
            1860                1865                1870
Leu Arg Phe Leu Gln Leu Leu Cys Glu Asn His Asn Arg Asp Leu Gln
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Asn Phe Leu Arg Cys Gln Asn Asn Lys Thr Asn Tyr Asn Leu Val Cys
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Glu Thr Leu Gln Phe Leu Asp Ile Met Cys Gly Ser Thr Thr Gly Gly
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Leu Gly Leu Leu Gly Leu Tyr Ile Asn Glu Asp Asn Val Gly Leu Val
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Ile Gln Thr Leu Glu Thr Leu Thr Glu Tyr Cys Gln Gly Pro Cys His
            1940                1945                1950
Glu Asn Gln Thr Cys Ile Val Thr His Glu Ser Asn Gly Ile Asp Ile
        1955                1960                1965
Ile Thr Ala Leu Ile Leu Asn Asp Ile Ser Pro Leu Cys Lys Tyr Arg
    1970                1975                1980
Met Asp Leu Val Leu Gln Leu Lys Asp Asn Ala Ser Lys Leu Leu Leu
1985                1990                1995                2000
Ala Leu Met Glu Ser Arg His Asp Ser Glu Asn Ala Glu Arg Ile Leu
                2005                2010                2015
Ile Ser Leu Arg Pro Gln Glu Leu Val Asp Val Ile Lys Lys Ala Tyr
            2020                2025                2030
Leu Gln Glu Glu Glu Arg Glu Asn Ser Glu Val Ser Pro Arg Glu Val
        2035                2040                2045
Gly His Asn Ile Tyr Ile Leu Ala Leu Gln Leu Ser Arg His Asn Lys
    2050                2055                2060
Gln Leu Gln His Leu Leu Lys Pro Val Lys Arg Ile Gln Glu Glu Glu
2065                2070                2075                2080
Ala Glu Gly Ile Ser Ser Met Leu Ser Leu Asn Asn Lys Gln Leu Ser
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Gln Met Leu Lys Ser Ser Ala Pro Ala Gln Glu Glu Glu Glu Asp Pro
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Leu Ala Tyr Tyr Glu Asn His Thr Ser Gln Ile Glu Ile Val Arg Gln
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Asp Arg Ser Met Glu Gln Ile Val Phe Pro Val Pro Ala Ile Cys Gln
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Phe Leu Thr Glu Glu Thr Lys His Arg Leu Phe Thr Thr Thr Glu Gln
2145                2150                2155                2160
Asp Glu Gln Gly Ser Lys Val Ser Asp Phe Phe Asp Gln Ser Ser Phe
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Leu His Asn Glu Met Glu Trp Gln Arg Arg Leu Arg Ser Met Pro Leu
            2180                2185                2190
Ile Tyr Trp Phe Ser Arg Arg Met Thr Leu Trp Gly Ser Ile Ser Phe
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Asn Leu Ala Val Phe Ile Asn Ile Ile Ile Ala Phe Phe Tyr Pro Tyr
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His Tyr Ser Val Arg Pro Leu Ile Val Ala Leu Val Leu Arg Ser Ile
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Tyr Tyr Leu Gly Ile Gly Pro Thr Leu Asn Ile Leu Gly Ala Leu Asn
        2275                2280                2285
Leu Thr Asn Lys Ile Val Phe Val Val Ser Phe Val Gly Asn Arg Gly
    2290                2295                2300
Thr Phe Ile Arg Gly Tyr Lys Ala Met Val Met Asp Met Glu Phe Leu
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Tyr His Val Gly Tyr Ile Leu Thr Ser Val Leu Gly Leu Phe Ala His
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Glu Leu Phe Tyr Ser Ile Leu Leu Phe Asp Leu Ile Tyr Arg Glu Glu
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Thr Leu Phe Asn Val Ile Lys Ser Val Thr Arg Asn Gly Arg Ser Ile
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Leu Leu Thr Ala Leu Leu Ala Leu Ile Leu Val Tyr Leu Phe Ser Ile
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Val Gly Phe Leu Phe Leu Lys Asp Asp Phe Ile Leu Glu Val Asp Arg
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Leu Pro Gly Asn His Ser Arg Ala Ser Thr Leu Gly Met Pro His Gly
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Ala Ala Thr Phe Met Gly Thr Cys Ser Gly Asp Lys Met Asp Cys Val
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Ser Thr Glu Arg Ala Cys Asp Thr Leu Leu Met Cys Ile Val Thr Val
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Met Asn His Gly Leu Arg Asn Gly Gly Gly Val Gly Asp Ile Leu Arg
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Lys Pro Ser Lys Asp Glu Ser Leu Phe Pro Ala Arg Val Val Tyr Asp
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Leu Leu Phe Phe Phe Ile Val Ile Ile Ile Val Leu Asn Leu Ile Phe
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Gly Val Ile Ile Asp Thr Phe Ala Asp Leu Arg Ser Glu Lys Gln Lys
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Lys Glu Glu Ile Leu Lys Thr Thr Cys Phe Ile Cys Gly Leu Glu Arg
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Asp Lys Phe Asp Asn Lys Thr Val Ser Phe Glu Glu His Ile Lys Leu
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Glu His Asn Met Trp Asn Tyr Leu Tyr Phe Ile Val Leu Val Arg Val
                2565                2570                2575
Lys Asn Lys Thr Asp Tyr Thr Gly Pro Glu Ser Tyr Val Ala Gln Met
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Ile Lys Asn Lys Asn Leu Asp Trp Phe Pro Arg Met Arg Ala Met Ser
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Leu Val Ser Gly Glu Gly Glu Gly Glu Gln Asn Glu Ile Arg Ile Leu
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Gln Glu Lys Leu Gly Ser Thr Met Lys Leu Val Ser His Leu Thr Ala
2625                2630                2635                2640
Gln Leu Asn Glu Leu Lys Glu Gln Met Thr Glu Gln Arg Lys Arg Arg
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<213> Artificial Sequence

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